Vol. XII. No. 6 Serial No. 62. November-December, 1928

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

CONTENTS

STUDIES OF THE ENDOCRINE GLANDS. VI. PLURIGLANDULAR SYNDROMES. Allan Winter Rowe and Charles Henry Lawrence, Boston 707

THE VAGINAL SMEAR METHOD OF ASSAY OF THE OVARIAN HORMONE. Lydia C. Kahnt and Edward A. Doisy, St. Louis 760

THE DISTRIBUTION OF THE OVARIAN HORMONE BETWEEN LIQUOR FOLLICULI AND THE RESIDUAL TISSUE. Sidney Thayer and Edward A. Doisy, St. Louis 769

THE THYROID GLAND IN INFECTIONS: THE EFFECT UPON THE BASAL METABOLIC RATE. N. A. Womack, W. H. Cole and A. G. Heideman, St. Louis... 773

PINEAL AND METAMORPHOSIS. THE INFLUENCE OF PINEAL FEEDING UPON THE RATE OF METAMORPHOSIS IN FROGS. John Addair and F. E. Chidester, Morgantown, W. Va. 791

A NOTE ON THE RELATION OF LIGHT TO THE ACTION OF PARATHYROID EXTRACT. Hector Rosello and L. M. Petrillo, Montevideo 797

A CASE OF DIABETES, REFRACTORY TO INSULIN, WITH HYPERPLASTIC AND ADENOMATOUS ADRENALS. Robert A. Moore, Columbus 800

OVARIAN AND PLACENTAL HORMONE EFFECTS IN NORMAL, IMMATURE ALBINO RATS. Geo. T. Golding and F. T. Ramirez, Columbia, Mo. 804

ABSTRACT DEPARTMENT. Containing 54 Titles and Articles Reviewed 813

Entered as second-class matter March 12, 1921, at the postoffice at Los Angeles, California, under the Act of March 3, 1879.

Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized September 17, 1920.

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

President.....OSCAR RIDDLE
First Vice-President.....PETER BASSOE
Second Vice-President.....EDGAR ALLEN
Secretary-Treasurer.....F. M. POTTENGER

COUNCIL

JOHN B. POTTS, *Chairman*, Omaha

L. F. BARKER, Baltimore
WM. ENGELBACH, St. Louis
J. EARL ELSE, Portland, Ore.
F. S. HAMMETT, Philadelphia
M. B. GORDON, Brooklyn
WALTER TIMME, New York
L. G. ROWNTREE, Rochester
L. R. DE BUYS, New Orleans
JOS. C. AUB, Boston
H. LISSER, San Francisco

Ex-Officio Members

OSCAR RIDDLE, Cold Spring Harbor, N. Y. R. G. HOSKINS, Boston
F. M. POTTENGER, Los Angeles

ANNOUNCEMENT

THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and organotherapy, and by concerted effort to broaden knowledge in this field.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators, in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's by-monthly bulletin.

The subscription price of ENDOCRINOLOGY to non-members is $6.00.

Further information and application blank may be secured by addressing the secretary, F. M. Pottenger, M.D., 1212-1214 Wilshire Medical Bldg., Los Angeles, California.

ENDOCRINOLOGY

EDITORIAL STAFF

R. G. HOSKINS, *Editor-in-Chief,* Boston

Associate Editors

MILTON O. LEE.....Harvard Medical School, Boston
H. LISSER.....University of California, San Francisco

E. ALLEN.....Columbia, Mo.
WAYNE J. ATWELL.....University of Buffalo
ARTUR BIEDL.....Prag, Czechoslovakia
E. BONILLA.....Madrid, Spain
ISRAEL BRAM.....Philadelphia
G. E. BURGET.....University of Oregon, Portland
T. C. BURNETT.....University of California, Berkeley
A. T. CAMERON.....University of Manitoba, Winnipeg
WALTER B. CANNON.....Harvard Medical School, Boston
G. CORONEDI.....Florence, Italy
JOHN C. DONALDSON.....Pittsburg
E. GLEY.....University of Paris
MURRAY B. GORDON.....Brooklyn
FREDERICK S. HAMMETT.....Wistar Institute, Philadelphia
MARGARET M. HOSKINS.....New York University
B. A. HOUSSAY.....University of Buenos Aires
H. J. JOHN.....Cleveland
KNUD H. KRABBE.....Copenhagen, Denmark
E. LARSON.....Chicago
G. MARANON.....Madrid, Spain
I. MCQUARRIE.....Detroit
P. M. NICCOLINI.....Florence, Italy
C. E. NIXON.....San Francisco
A. T. RASMUSSEN.....Minneapolis
C. I. REED.....Dallas
A. W. ROWE.....Boston
EDWARD SHARPEY SCHAFER.....University of Edinburgh
J. P. SIMONDS.....Northwestern University Medical School, Chicago
G. VERCELLINI.....Los Angeles
SWALE VINCENT.....Middlesex Hospital, London

ENDOCRINOLOGY is the official bulletin of the Association for the Study of the Internal Secretions. It is published in volumes of 600-800 pages. At present it appears as a bimonthly. It comprises original articles, authoritative reviews, critical abstracts of the endocrine literature and editorial discussions of timely topics.

Manuscripts of three types of original work are desired for publication:

a. *Clinical studies* of endocrine diseases and the part played by the endocrine organs as contributing factors in other diseases;

b. *Systematic studies* on endocrine therapy;

c. *Laboratory investigations* of endocrine problems.

Articles are accepted for publication with the understanding that they will appear in this journal only.

Manuscripts may be submitted in any modern language, and if found suitable for publication will be translated into English without expense to the authors. To insure a version, however, satisfactory to the author, it is desirable that the article be submitted, when feasible, in English.

Readers who encounter articles of endocrine interest in unusual periodicals or under captions not indicating such interest are requested to submit abstracts for publication.

Bibliographic form: Since ENDOCRINOLOGY is to a considerable extent a bibliographic journal, it is desirable that references should be given in *complete form,* quoting title of article, author, periodical, year, volume number and page. The references should be segregated on separate sheets for publication at the end of the article. Footnotes should be used sparingly and included with the text.

Illustrations: A reasonable number of illustrations suitable for zinc line reproductions may be included. Half-tone reproductions will ordinarily necessitate a reasonable charge to the author.

Reprints: One hundred will be furnished gratis. For larger quantities price list and order blank will be sent with galley proof.

Subscriptions and remittances should be sent to the Secretary-Treasurer of the Association, Dr. F. M. Pottenger, 1212-1214 Wilshire Medical Bldg., Los Angeles, Calif.

Manuscripts may be addressed to the Editor, Prof. R. G. Hoskins, Harvard Medical School, Boston, 17, Mass., or to any of the members of the staff.

Correspondence relating to advertising and business matters should be addressed to Endocrinology, 1212-1214 Wilshire Medical Bldg., Los Angeles, Calif.

VOLUME XII.

This number of ENDOCRINOLOGY completes Vol. XII. As usual, the index for the entire volume will be found at the close of this number, following the Abstract Department, the authors and subjects being in separate sections.

Title Page and Table of Contents will be found just preceding page 707 of this number. This is a separate signature and can be removed to its proper place when binding.

VOLUME 13.

Beginning with Vol. 13 a number of changes will be made in the make-up of this journal. Chief among these will be the increase in page size to 7x10½ inches. This will afford opportunity to present many tables, charts and illustrations to a better advantage than at present.

OUR NEXT ANNUAL MEETING

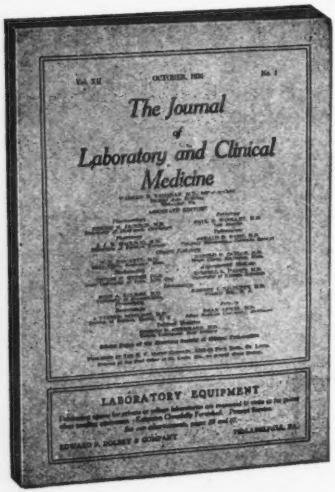
Arrangements have been completed for the holding of our next annual meeting, Tuesday, July 9, 1929, in The Auditorium, Portland, Oregon. More definite announcement of this will be made in a later issue of ENDOCRINOLOGY.

IMPORTANT NOTICE—CHANGE OF ADDRESS

The offices of the Secretary-Treasurer of The Association for the Study of Internal Secretions, and of ENDOCRINOLOGY, have been moved to the new Wilshire Medical Building at the corner of Wilshire Blvd. and Westlake Avenue. The new address is 1212-1214 Wilshire Medical Building. All correspondence should now be thus addressed.

The Journal of Laboratory and Clinical Medicine

Published first of each month. Volumes begin with October of each year. Subscriptions may begin at any time. $8.50 per year under domestic postage, including the United States, Cuba, Mexico, Porto Rico, Canal Zone, Hawaii, and Philippines. Under Canadian and foreign postage, $8.90. Single copies, 75 cents.



Important Features

1. The only journal devoted exclusively to the laboratory and to clinical medicine. Official organ of American Society of Clinical Pathologists and the American Association of Allergy.

2. Under direct editorial supervision of Dr. Warren T. Vaughan, and thirteen associate editors, representing leading medical schools and hospitals of America.

3. Only original, timely articles passed upon by editorial board accepted for publication.

4. Special department on laboratory methods, giving new methods and appliances for the laboratory.

5. Abstracts of articles from leading periodicals of the entire world.

6. Editorials by the editorial staff on timely subjects appear in each number.

7. Each volume contains almost 1,000 pages of up-to-date literature, with many beautiful illustrations in black and white and sometimes in colors.

EDITORIAL BOARD

WARREN T. VAUGHAN, Editor-in-Chief

DENNIS E. JACKSON
JOHN A. KOLMER
VICTOR C. MYERS
J. J. R. MACLEOD
W. C. MacCARTY
RUSSELL L. HADEN
PAUL G. WOOLLEY
ROBERT A. KILDUFFE
HAROLD C. CAYLOR
A. PARKER HITCHENS
DEAN LEWIS
GERALD B. WEBB
GEORGE R. HERRMANN

(Endocrinology)

THE C. V. MOSBY CO., 3523-25 Pine Blvd., St. Louis.

Gentlemen: Enter my subscription to the **Journal of Laboratory and Clinical Medicine,** annual subscription rate in U. S. and U. S. Postal Zone, $8.50. You may send me bill with first issue.

Name.....

Address.....

E. SH
J.

BRISCOE, GRACE, Experimental Prod
tractions of Natural Form in the Diap

REID, CHARLES, The Mechanism of Volu

KENNEDY, WALTER P., and DAVID R. CLIMEN
Blood of Birds.—I. The Corpuscles of the Pigeon

SMITH, J. LORRAIN, and THEODORE RETTIE, The Ab
Deposition, and Transport of Fat in the Guinea-pig

DRYERRE, HENRY, The Influence of Thyroid Preparations upon the Cardiac and Vascular Nerves 61

SHARPEY-SCHAFER, E., The Effects of De-nervation of a Cutaneous Area 85

The price of this Number is Ten Shillings and Sixpence.
Papers for publication may be sent to any of the Editors.

CHARLES GRIFFIN AND COMPANY, LIMITED
42 DRURY LANE, LONDON

...its
...rac-

...v you
...sults in

Spleenmar-
and complete

...ABORATORIES your guarantee"

...21 S. Western Boulevard
Chicago, Ill.

Manufacturers of
STANDARDIZED ANIMAL DERIVATIVES, LIGATURES AND
DIGESTIVE FERMENTS

(COUPON)

THE WILSON LABORATORIES,
4221 S. Western Blvd., Dept. E,
Chicago, Ill.

Gentlemen: Please furnish me, free of charge, material and particulars of your Spleenmarrow proof.

I am also interested in learning about Liver Extract (Wilson) Capsules.

Check here ☐

Dr.....

Address.....

.....

Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

November-December, 1928

STUDIES OF THE ENDOCRINE GLANDS
VI. PLURIGLANDULAR SYNDROMES

ALLAN WINTER ROWE, Ph.D.
and
CHARLES HENRY LAWRENCE, M.D.
Evans Memorial
BOSTON, MASS.

In a series of previous communications the details of an objective method for the differential diagnosis of endocrine disorders have been reported (1) and the results collected which have been obtained by its application to certain members of the ductless glandular group.*

The present paper deals with a small group of cases (22) in which morbidity of more than one endocrine focus was capable of demonstration—in other words, the so-called pluriglandular syndromes. Readers of the earlier papers of this series will have surmised that the authors do not subscribe to the current orthodox idea of the frequency and significance of the conditions thus designated. The present meager group represents the careful selection from a series of nearly four thousand patients

*Rowe and Lawrence (Pituitary) (2); Lawrence and Rowe (Thyroid) (3); Rowe and Lawrence (Gonad) (4).

examined, and are the only ones seemingly in which multiglandular involvement could be certainly demonstrated. This does not imply that in a large number of endocrine cases evidence of impaired function will not be found in endocrine centers other than that in which the basic condition finds its origin. But these manifestations are purely secondary and as much the result of the general metabolic disturbance as are the concomitant malfunctions of a large group of non-endocrine entities. Further, there can be but little question that primary functional disturbance of rigorously non-endocrine tissues will engender perverted activities of the endocrine group as components of the complete human mechanism. The authors' position may be summarized as a sincere desire to separate cause from effect and to avoid the endowment of sequelae with the authority of a primary causative significance. To illustrate with but one example from the many, it is a frequently recorded fact that serious malfunctions of either the pituitary or the thyroid engender, among many other symptoms, an impairment of the menstrual function. This may become a true amenorrhœa in cases of established gravity. Though the menstrual function presumably has its origin in certain of the cells composing the ovary, and is an external manifestation of an exocrine activity, the popular opinion that regards the control of this function as implicit in the internal secretory activities rests, after all, upon certain assumptions which are not entirely based upon controlled objective facts to support it. Amenorrhoea may exist with seemingly normal ovarian endocrine activity, and patients with severe gonad failure may exhibit normal menstrual function. Castration and transplantation experiments are not germane to the thesis, as all portions of the gland inevitably participate.

The assumption, then, that a pituitary or thyroid amenorrhoea implies a primary participation of the internal secretory activity of the ovary is the result of an elaborate synthesis of unsupported speculations which have, however, been so frequently repeated as to assume with many the authority of established fact. Sight is lost of the fact that with no valid evidence of an interdependence between endo- and exo-crine functions, one rather sweeping assumption becomes vital to the thesis. In this connection, as stated above, we have frequently observed

amenorrhœa with no objective evidence of other than normal ovarian function, and equally, many subjects have been studied demonstrating a definite gonad failure and reporting an entirely normal menstrual history. Only in those anatomical and structural changes in which all portions of the gland participate, do we necessarily find simultaneous inhibition of both internal and external activities. To go but one step further, the existence of amenorrheas of a rigorously non-endocrine origin is generally recognized, as those, let us say, of cardiac or renal origin. If the multiglandular theory be adopted, it becomes necessary to infer a primary gonad failure in these conditions, a conclusion which is not only devoid of any supporting evidence, but against which an impressive array of observed and tested facts can be marshalled. This constitutes a second vital flaw in the chain of speculative reasoning. Without dwelling further on this phase of the topic, it may be said that objective fact imposes straiter limits than does subjective theory.

The advocates of pluriglandular doctrine range from those who see in every phase of endocrine malfunction an algebraic summation of disturbed activity of all the members, established and putative, of the family of ductless glands,* while others, with a larger measure of conservatism, restrict the concept to those more or less well defined disease pictures which are frequently designated by the names of their proponents.† These represent extremes of thought, and between them is found a protean array of intermediate theories. That the polypharmacy of the manufacturing drug houses has played an important role in confirming an uncritical acceptance of the general concept, must be recognized.§ The scientific warrant for the administration of a complex mixture of glandular extracts is certainly tenuous, and the exhibition of a combination containing ovarian

*In the first group (among others, Keith [5], and Berman [6], should be numbered those writers who courageously discount all cosmic influences and regard ethnic types as determined physically and psychically by intriguing permutations of function in which the whole endocrine family participates. It is unfortunate for the general acceptation of these broad and stimulating generalizations that no objective evidence has as yet been adduced that offers the faintest support.

†In this category fall the "multiple ductless glandular sclerosis" of Falta (7), Timme's (8) "thymus-adrenal-pituitary" compensatory syndrome, and the numerous complexes suggested by the clinical workers of France.

§The reductio ad absurdum has recently appeared in a widely circulated device with which by means of a slotted rotating disk any given symptom can be mechanically correlated with the correct pluriglandular preparation designated by number. As a basis for diagnosis and treatment this compares well with a crystal ball or the intricate arrangement of tea leaves.

and mammary substance to the male sufferer conjures up pleasing vistas of speculation.*

To avoid misunderstanding, a statement in the earlier part of this paper must be reiterated. Many of the existing contradictions and disagreements concerning multiglandular disease rest on the artefactual basis of a question of terminology. The endocrine glands, those at least whose warrant to this designation has been clearly indicated, are among the important regulators of general body metabolism. In the enormously intricate interlocking directorate of the animal mechanism there exist an unguessable number of balanced and delicately adjusted equilibria. The existence of protective compensatory mechanisms forms a necessary corollary to the initial concept and these provide for readjustments to meet the constantly changing conditions inherent in the life processes. With a serious derangement, from whatever cause, such compensations are perhaps not effective, or at the best, only partially so. A pertinent and relatively simple illustration of this point is offered by the regulation of the hydrogen ion concentration of the blood shown in health and disease. Intricate though it be, present knowledge would indicate for it a far greater simplicity than for many other necessary functions which physiology is defining and interpreting. When a disturbed condition arises, many of the functional equilibria are influenced, not in equal measure but in varying degrees. Such changes of level engender others, and in these ramifications of an initial impulse, a vast number of end results will appear in the form of more or less profoundly altered functional levels. Frequently, as we see in any well characterized syndrome, a certain group of common manifestations will be engendered, differing among themselves in degree but not in kind. Contextually, a horde of minor divergences become manifest, portraying the influence of individual difference. As a corollary to this we should equally expect one cer-

*Happily many of these preparations are practically inert and their administration allows of all possible psychic benefit without physical injury. Occasionally cases present, however, where this negative benefit does not obtain, and acute conditions have arisen from injudicious use. The greatest single need in the field of glandular therapy today, is the single substance whose physiological activity has been standardized by some dependable biological method of assay. Some progress has been made but much remains to be done. The determination of the iodine content of a thyroid preparation as an index of activity is on a parity with the standardization of digitalis by an estimation of the glucose content. Further discussion is unnecessary here since a paper treating this whole question is shortly to appear.

tain end result, of well defined character, to arise from a wide diversity of causes. The same illustrative mechanism already noted will serve to exemplify this point. Acidosis, an end result, is the increase of the hydrogen ion concentration of the blood. The many divergent origins producing this single final product are too well known to require statement. Any given symptom may be a result of any one of a number of wholly dissociated initial causes, and this fact should never be ignored in establishing relationship between effect and cause. Causal elements must be individually evaluated and the final allocation be determined by exclusion.* With the endocrine glands integral and in some cases essential factors in the body complex, it is obvious that disturbed function in one of them, from whatever cause, will engender resultant disturbances in other members of the group. Equally, however, in the breaking down of normal relationship, a whole series of other foci of control will be subversively affected and their functional levels likewise exhibit change. In this sense, we have pluriglandular disease, but to preserve a just parity, we must apply the same term to those conditions of non-endocrine origin in which the ductless glands participate as secondary and resultant stadia in the progress of the condition. The adoption of such a just and equitable classification would hardly prove constructive in the diagnosis and treatment of disease. Differentiation is the prime requisite, and the larger the measure of specialized function, the greater the opportunity for eliminating, or more usually, partly inhibiting superimposed extraneous influences. Man, rather than the amoeba, is the subject of election for functional study.

Recognizing a mutual interdependence of the ductless glands—in common with all other parts of the mechanism—it is only to that assumption of special esoteric interrelationship as implicit in this single group to which the authors take exception. And the ground upon which this opinion rests is the careful study, by purely objective methods, of individuals in whom a presenting disorder was the result of demonstration and not of inference. If, for example, as a uniform and unvarying result of the removal of the ovaries in adult womanhood and before the menopause, it is observed that the power of assimila-

*The present method of differential diagnosis is based on the principle, with the added factor that the endocrine element comes to consideration only after possibly causal non-endocrine disease has been eliminated by test and observation.

tion for galactose is reduced by 50 per cent, one is warranted in assuming that some relationship seemingly exists between carbohydrate metabolism and an influence exercised by the presence or absence of these glands. Such a fact has diagnostic significance when supported by an adequate number of other tested facts. Finally, the authors wish to emphasize that at no time do they deny the possible existence of a true pluriglandular involvement. With the numberless permutations and combinations possible, it would indeed be remarkable if cases did not exist in which a simultaneous primary malfunction was exhibited. In the present series there are a few cases in which such a condition seems to obtain. With such cases, however, as infrequent as they have been found to be, we tentatively suggest that their pluriglandular designation may derive from our own imperfect knowledge rather than from a true multiple involvement. In any case, in our experience, true pluriglandular syndromes, if they exist, are seemingly of the greatest rarity.

It is not necessary to protract this discussion further. Additional supporting evidence for the general thesis constitutes a part of the papers which have already appeared. Further, there is every reason to believe that among many workers in this field the term "pluriglandular" is used in the same restricted sense that here obtains.

Turning to the component members of this series, a necessary preliminary statement is the designation of the individual case with indication of the glands involved. These facts are presented in Table I. (See next page).

Of the 22 cases here listed, 17 owe their plurality to the coexistence of a functional error in one gland with the result of surgical alteration of another endocrine focus. Of these, 14 are complete castrates, while 4 were postoperative cases after thyroidectomy. The seeming arithmetical contradiction, as inspection of the table will show, depends upon one case with surgical intervention in more than one gland. In the light of the previous discussion, the five remaining cases offer a peculiar point of interest. As they will be discussed in detail in the body of the paper, it may be briefly stated that cases B-532 and B-37 are the only ones in which some modifying circumstance does not present. B-18, seen in early middle life as a thyroid fail-

ure, had had a pituitary hyperfunction in prepubertal years with some evidence of a residual posterior lobe overactivity. Her inclusion in the group is partly conventional. S-568 is a frankly doubtful case, the thyroid dysfunction determining her presenting symptoms and the pituitary element resting primarily on the very dubious ground of a seemingly distorted sella. S-686 was a partial castrate and falls between the disease and surgical groups.

TABLE I

GLANDS INVOLVED WITH CHARACTER AND ORIGIN OF DERANGEMENT

Group	Case Number	Function	Pituitary			Thyroid		Ovary	
			Ant.*	Post.	Origin	Func.	Origin	Func.	Origin
I—a	B-37	dys.	—	—	Dis.	—	Dis.		
b	B- 18	dys.	—	+	Dis.	—	Dis.		
	B- 532	dys.	—	+	Dis.	—	Dis.		
c	B- 141	dys.	N or —	+	Dis.	±	Surg.		
	S- 568	dys.	N or —	+	Dis.	±	Dis.		
II—a	B- 659	hypo	—	—	Dis.			—	Surg.
	S- 744	hypo	—	—	Dis.			—	Surg.
	S-1327	hypo	—	—	Dis.			—	Surg.
	S-1343	hypo	—	—	Dis.			—	Surg.
	S-1669	hypo	—	—	Dis.			—	Surg.
III—a	S- 686	hypo				—	Dis.	—	Dis.
	B- 109	hypo				—	Dis.	—	Surg.
	B- 599	hypo				—	Dis.	—	Surg.
	B- 662	hypo				—	Dis.	—	Surg.
	B- 976	hypo				—	Dis.	—	Surg.
	S-1843	hypo				—	Dis.	—	Surg.
b	S- 179	dys.				±	Surg.	—	Dis.
	S- 230	dys.				±	Surg.	—	Surg.
	S- 988	dys.				±	Dis.	—	Surg.
	S-1023	dys.				±	Dis.	—	Surg.
	S-1069	dys.				±	Dis.	—	Surg.
IV—a	B- 164	dys.	?	+	Dis.	±	Surg.	?—	Surg. Dis.

*The indicated functional levels of the anterior lobe are tentative and based on probability.

The presentation of our data in tabular form, never entirely satisfactory, is peculiarly hampered in the present instance. With the permutational possibilities on the one hand, and the frequently contrary effects of the several malfunctions on the other, the salient differences shown by the individual cases merge when summated in an average. Some of the cases fortunately present sufficient similarity to make averages typical. In the Pituitary-Thyroid group this helpful condition is lacking. As the individual protocols form a part of this paper, in the inter-

est of economy of space and a just recognition of the intrinsic limitations, we have merged these cases into three sub-groups which are not wholly dissimilar.

In the following discussions, cases will be designated as "hypofunctional" (—) in which all of the observations indicate lowered activities of the glands involved, while "hyperfunction" (+) indicates the antithetical condition. "Dysfunctional" (±) cases are those where evidence of both phases of activity are seemingly present in a single gland, or where the two glands are at different functional levels. The authors adopt this convention—which is not devoid of sanction—to avoid unproductive and space-consuming dialectic. The definition, at least, permits the reader to visualize the symptom complex.

In the subsequent tabulations, Case B-976 in Group III-a will be omitted. This patient is the only male in the entire series, and his inclusion would only add one more disturbing element to the difficulties of collective presentation.

TABLE II

PHYSICAL MEASUREMENTS

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	±	—	—	±	±
	—	—	±	—	—	—	
Number of Cases	2	2	2	5	5	5	1
Age, Av. (yrs.)	51	36	53	49	42	44	40
Height, Av. (cm.)	166	177	171	158	165	160	147
Sitting Height, Av. (cm.)	86	92.5	89.5	86	88	87	81.5
Sitting Height, Index	0.518	0.523	0.523	0.544	0.533	0.544	0.554
Chest, Av. (cm.)	107	89	87	81	76	79.5	80
Weight, Av. (kgm.)	106.2	84.4	70.6	63.1	61.9	67.6	59.8
Area, Av. (sq. m.)	2.13	2.00	1.87	1.64	1.68	1.70	1.52
Lung Volume, Av. (cc.)	1720	3620	2600	2260	2720	2440	2000

Table II contains certain statistics and, incidentally, as measurements are absolute, realizes the worst possibilities of this method of presentation. The dominance of castration as a source of plurality determines the large incidence of cases with gonad involvement. The average ages are higher—well over forty as opposed to the low thirties of the other groups already

described. The greatly lessened incidence of surgical intervention with the endocrine glands in childhood, is probably the determining factor. The average heights are not remarkable, the six feet three inches of B-18 being partly merged in a less conspicuous total. The pituitary cases would seem to have a slight upward tendency, however. Sitting height indices show some variation, the more significant as the whole series is confined to one sex. The single case in Group IV gives a value suggestive of achondroplasia, and those in II-a and III-b are definitely above the normal. Pituitary, reinforced by thyroid, determines an obesity suggested only in one sub-group of the

TABLE III

"VITAL CAPACITY" MEASUREMENTS

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	±	—	—	±	±
	—	—	±	—	—	—	
Weight—							
High (%)		+24	+14	+52	+31	+36	
Low (%)		— 3	+12	— 5	— 4	— 5	
+ Average (%)		+24	+13	+21	+31	+14	
Percent of Group		50	100	60	20	80	
— Average (%)		— 3	—	— 3	— 9	— 5	
Percent of Group		50	0	40	80	20	
Net Average (%)	**+78**	**+11**	**+13**	**+12**	**— 1**	**+10**	**+22**
Chest—							
High (%)		+23	+16	+22	+20	+30	
Low (%)		∓ 0	+ 7	+ 5	—18	— 4	
+ Average (%)		+12	+12	+ 8	+12	+12	
Percent of Group		100	100	100	40	60	
— Average (%)		—	—	—	—12	— 4	
Percent of Group		0	0	0	60	40	
Net Average (%)	**+43**	**+12**	**+12**	**+ 8**	**— 3**	**+ 6**	**+12**
Lung Volume—							
High (%)		+ 3	—24	—16	— 2	—14	
Low (%)		— 9	—28	—39	—36	—40	
+ Average (%)		+ 3	—	—	—	—	
Percent of Group		50	0	0	0	0	
— Average (%)		— 9	—26	—28	—18	—24	
Percent of Group		50	100	100	100	100	
Net Average (%)	**—48**	**— 3**	**—26**	**—28**	**—18**	**—24**	**—29**

Thyroid-Gonad combination. The lung capacities give evidence only of a general influence, and the other data reflect the height and weight relations. As is to be expected, every effort to formulate relative influences in mathematical terms has been

unproductive. Possibly with large groups (fifty or more) presenting closely related functional levels in each combination, statistical analysis might yield a first approximation. Only a later generation will have adequate data. The application of the method of least squares to a few cases is not even a diverting mathematical pastime.

With properly established standards, comparative values enjoy a significance of which the absolute raw data are devoid. Such a comparison, under conditions already described (1), are found in Table III.

The Pituitary obesities are here more strikingly indicated, although curiously enough three castrates with bilobar failure exhibit weights closely in accord with prediction. The small number of cases prevents the observation from being more than interesting. The chest comparisons logically repeat those on weight. All of the groups except I-b show a lowered lung capacity. The pluriglandular group is the lowest of our several series. Seemingly the double burden plays a part.

TABLE IV

URINE MEASUREMENTS

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	±	—	—	±	±
	—	—	+	—	—	—	
Volume.....Av. (cc.)	2650	1300	1430	1470	1410	1130	1600
Specific Gravity.....Av.	1.008	1.018	1.022	1.014	1.013	1.017	1.014
Albumin.....(%)	100	100	0	40	40	60	100
Casts.....(%)	0	50	0	0	0	0	100
Sugar.....(%)	0	0	100	0	0	20	0
Salol.....Av. (min.)	165	85	60	—	85	—	60
P. S. P. Elim...Av. (%)	60	54	56	53	51	59	50

The urine data of Table IV offer a few points of interest.

A depressing effect on urine volume of thyroid and ovary is possibly reflected in the total group averages which are, I—1620 cc., II—1470 cc., and III—1270 cc. Less certainly can be traced a thyroid influence on the appearance of albuminuria, the relative percentages being, I—60, III—50, and II—40. A

posterior lobe failure apparently compensates for the glycosuric effect of castration in Group II no more than does the hypoactive thyroid in Group III-a. The indications of the phthalein test are not remarkable.

The Nitrogen Partition values (Table V) might be interpreted as indicating an increased influence of the Gonad over Pituitary and Thyroid in the production of a high Residual fraction. Comparison with the data from the series of uni-

TABLE V

NITROGEN PARTITION

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Total Nitrogen, Av. (gms.)	12.17	9.20	9.84	9.17	7.03	10.02	9.71
Urea Nitrogen...Av. (%)	81.1	80.5	76.7	78.6	80.4	80.6	89.7
Uric Acid Nitrogen Av. (%)	2.4	2.5	4.6	2.1	2.1	2.1	1.5
Ammonia Nitrogen Av. (%)	4.6	6.2	2.0	4.3	4.8	4.2	3.6
Creatinin Nitrogen Av. (%)	4.4	5.4	4.5	4.6	4.8	3.8	3.1
Residual Nitrogen Av. (%)	7.5	5.4	12.2	10.4	7.9	9.3	2.1
% = or above 9%	0	0	100	60	20	60	0

glandular involvements in the preceding papers shows this not to be the case, however. The values here signify no more than that the metabolic error reflected in a high residual nitrogen is shown by all of the endocrines—and other studies betray a similar result in a fairly large group of non-endocrine diseases.

The chemistry of the blood, as presented in averages (Table VI), offers but little information. The relative uric acid increase, which is characteristic of uncomplicated pituitary malfunctions, is here not strikingly present (30 per cent in pituitary as against 20 per cent in non-pituitary cases). We record the fact without offering explanation. Residual nitrogen values assume significant heights only in the single case of Group IV. That this latter should exhibit it is not surprising in the light

of her chronic interstitial nephritis and diverse endocrine pathology. The blood sugar sequence is not remarkable, the lower value in the Hypo-Thyroid-Gonad group being probably fortuitous.

TABLE VI

BLOOD CHEMISTRY

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Non-Protein Nitrogen Av. (mgm.)	38	30	31	32	33	34	44
Urea Nitrogen Av. (mgm.)	19	16	16	15	16	17	21
Uric Acid Av. (mgm.)	5.0	3.2	3.4	3.6	3.6	4.0	6.0
Net* % = or above 4 mgm.	0	50	0	20	20	20	0
Creatinin Av. (mgm.)	1.9	1.4	1.4	1.5	1.5	1.5	1.4
Residual Nitrogen Av. (mgm.)	16.7	12.3	13.3	15.2	15.2	15.1	20.5
Sugar (mgm.)	127#	97	99	98	87	103	97

*All cases demonstrating nephritis have been deleted.
#Value too high. Patient was very obese and blood obtained with difficulty.

In the Blood Morphology (Table VII), two or three apparent relationships present. The tendency toward a secondary anaemia of Groups II and III, and the higher level of the lymphocytosis in Group III, are probably apparent rather than real. The association of an eosinophilia with the pituitary cases harmonizes with the observations with the uncomplicated cases. No record of serological findings is tabulated, as the response to the several tests was uniformly negative.

With the data of the Respiratory Metabolism (Table VIII), we find almost for the first time clear evidences of the summation effects of the several glands. This is probably due to the fact that again we are dealing with relative values, and the several magnitudes assume a concrete significance through the use of a standard of comparison allowing for individual variation. With the thyroid recognized as the primary regulator of

the basal rate—at least in the group under consideration—with the pituitary and gonad on a basis of approximate parity—the pituitary perhaps slightly more effective—we should expect to find real differences. Pituitary and Thyroid failure together determine the lowest level, and while the dominance of the Thyroid is again manifest in the Thyroid-Gonad failures, Pituitary and Gonad together cannot lower rates to the depth which participation of the Thyroid connotes. Equally, antagonistic levels

TABLE VII

BLOOD MORPHOLOGY

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	±	—	—	±	±
	—	—	+	—	—	—	
Haemoglobin....Av. (%)	**100**	**90**	**88**	**86**	**89**	**83**	**100**
Color Index	0.76	0.94	0.84	0.88		0.90	0.90
Erythrocytes....Av. (10^6)	**6.56**	**4.80**	**5.22**	**4.87**	**4.77**	**4.59**	**5.56**
Leucocytes ....Av. (10^3)	**10.0**	**7.4**	**5.6**	**8.9**	**8.2**	**8.2**	**7.9**
P. M. N. Neutrophiles							
Av. (%)	**60**	**56**	**54**	**57**	**55**	**46**	**57**
% =or above 75%.....	0	0	0	20	0	0	0
Lymphocytes...Av. (%)	**34**	**35**	**39**	**35**	**36**	**49**	**37**
% =or above 33%.....	100	50	100	60	60	100	100
Eosinophiles.....Av. (%)	**1**	**2**	**2**	**4**	**2**	**1**	**1**
Net* % =or above 3%	0	50	50	40	20	0	0
Monocytes.....Av. (%)	**5**	**6**	**5**	**4**	**7**	**4**	**5**

*All cases demonstrating a non-endocrine cause of eosinophilia have been deleted.

are strikingly shown in the several dysfunctional groups. The single case in Group IV probably shows a residual hyperactivity of the thyroid which compensates the depressing effect of the conjoint gonad and anterior lobe failures. Blood Pressures and Pulse Rates show similar tendencies but without the clarity of definition of the Basal Rate measurements. As noted in the table, a single hypertensive case in any one of these very brief series influences the group average unduly. The effect of the Gonads on Alveolar Carbon Dioxide is not strikingly exhibited in the presence of either the Pituitary or of the Thyroid.

As with the Respiratory Metabolism, the additive character of the carbohydrate influences gives a true significance to certain of the collective averages. For the sake of clarity, the

reader may be reminded that the level of tolerance for galactose for the normal adult female is at forty grams. Castration or severe functional failure of the gonads lower this to twenty grams, less severe to thirty, the stadia being determined by the conditions of applying the test and not implying abrupt transitions. The posterior lobe of the pituitary may condition, by overactivity, a complete extinction of the tolerance, or equally, by a lowered function may raise it 200 per cent or more. With the thyroid, the sense of the change follows the pituitary, but the magnitude varies widely and significantly. Over two-thirds of the thyroid cases show a normal tolerance (for galactose), and the remainder exhibit changes of the order of ±33 per cent. Finally, in the normal sex cycle immaturity connotes the

TABLE VIII

RESPIRATORY METABOLISM

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	—	±	±	—	—	±	±
	—	—	±	—	—	—	
Basal Metabolism							
Deviation—High...(%)		—22	— 3	— 7#	—21	— 6	
Low....(%)		—44	—25	—23	—30	—14	
Average.....(%)	—34	—33	—14	—20	—26	—11	— 1
Blood Pressure							
Systolic....Av. (mm.)	128	106	161*	106	117*	104	165
Diastolic....Av. (mm.)	80	71	81*	66	72*	72	110
Pulse Rate Av. (per min.)	72	56	80	64	61	81	84
Respiration Rate							
Av. (per min.)	20	12	11	14	15	13	16
Temperature....(deg. F.)	97.8	98.2	97.7	97.7	97.1	98.6	98.0
Alveolar CO_2..Av. (mm.)	46	43	37	41	39	42	33
% less than 35 mm.....	0	0	50	0	0	20	100

#Value too high. Patient was nervous. Omitted in deriving average.
*A single case of hypertension influences the average unduly.

same level as that of castration, while the menopause may produce no change or more usually a depression to thirty grams. The data derived from the application of this test are given in some detail in Table IX.

A closer analysis of the sub-groups is most informative. In the first (I-a), a single case, pituitary underactivity raises the tolerance 100 per cent. In the second (I-b), the depressing influ-

ence of the posterior lobe outweighs the upward thyroid tendency, and the result is a depression of moderate degree. In the dysfunctional Pituitary-Thyroid section (I-c), the Thyroid inhibition of the Pituitary depression is lessened, and the low level of —83 per cent is realized. In Group II, castration has lowered the tolerance to twenty grams, and the more powerful augmenting power of posterior lobe failure on assimilation capacity raises the tolerance over 100 per cent above prediction.

TABLE IX

GALACTOSE TOLERANCE

Group	Case Number	Function			Galactose Tolerance			Group Average
		P (post.)	T	G	Normal	Observed	Deviation	
I—a	B- 37	—	—		30	60	+100	+100
b	B- 18	+	—		40	30	— 25	— 38
	B- 532	+	—		40	20	— 50	
c	B- 141	+	±		30	5	— 83	— 83
	S- 568	+	±		30	glycosuria	?	
II—a	B- 659	—		—	20	60	+200	
	S- 744	—		—	20	30	+ 50	
	S-1327	—		—	20	40	+100	+110
	S-1343	—		—	20	40	+100	
	S-1669	—		—	20	40	+100	
*III—a	S- 686		—	—	40	30	— 25	
	B- 109		—	—	20	20	± 0	
	B- 599		—	—	20	30	+ 50	+ 13
	B- 662		—	—	20	30	+ 50	
	B- 976		—	—	30	30	± 0	
	S-1843		—	—	20	20	± 0	
b	S- 179		±	—	40	10	— 75	
	S- 230		±	—	20	glycosuria	?	
	S- 988		±	—	20	10	— 50	— 19
	S-1023		±	—	20	20	± 0	
	S-1069		±	—	20	30	+ 50#	
IV—a	B- 164	+?	±	—	40	10	— 75	

*Note inclusion of Case B-976.
#Marked Thyroid failure under heavy medication at time of test and included in dysfunctional group for this reason.

	Unweighted Averages	
	Hypo-	Dys-
P + T	+100	—60
P + G	+110	—
T + G	+ 13	—19
P + T + G	—	—75

Turning to Group III—Thyroid and Gonad—the first case in sub-group "a" is a possible functional ovarian failure superimposed on a hypofunctional thyroid. This determines a slight lowering from the normal level. The second and sixth cases

were castrates with a functional hypothyroidism that did not affect the tolerance, while in the third and fourth the magnitude of the thyroid depression raised the tolerance 10 grams above the level determined by the castration. The fifth case, the only male in the entire series, shows a normal tolerance, the thyroid failure not being sufficient to raise the assimilation limit, and the castration being devoid of influence on this function. The divergent tendencies are more variably expressed in the individual members of Group III-b, which is not entirely uniform in its composition. For example, in Case S-179, a functional gonad failure and thyroid dysfunction (surgical), the one influence supplements the other and produces a level 75 per cent below prediction. On the other hand, Case S-1069 by castration has a predicted level of twenty grams, but the superimposed thyroid failure raises the assimilation limit to thirty, or an increase of 50 per cent. This latter subject was under drastic thyroid medication and in spite of this the basal rate was still —12 per cent. As was discussed at some length in the thyroid paper, we have some reason to believe that this gland produces more than one active principle, and that while the energy regulating hormone —thyroxin or something similar—may be supplied in exact measure, another agent which influences the carbohydrate tolerance may be simultaneously either in excess, equal amount or deficit. The other tolerances observed in the group are those which could be predicted from the algebraic sum of the several agencies operative.

This concludes the presentation and discussion of the more salient points elicited by the laboratory examination. Many other observations were made with each patient but their nature precludes presentation in summarized tabular form.

To conclude this discussion, a few of the characteristic influences are sufficiently salient to manifest themselves even under the inhibiting conditions of tabular presentation. These are, in the main, the relative values resulting from comparison with standards absorbing individual variation or, as in the case of the galatose tolerance, where additive relations exist. The results of the special clinical observations of the Consulting Staff adapt themselves even less well than do the laboratory data to the tabular form of presentation.

The characteristic features of disturbance of the individual glands has already been adequately covered in the previous papers. While the protocols of each case will be given later in the paper, a few of the clinical data may, for the sake of convenience, be collated for discussion. In the main, such analysis is unprofitable, as the factors of variation are too many to make collective consideration significant. The exceptions will be dealt with in the next section.

Part II

Note has already been made of the relatively greater age of this group at the time of first admission to the Clinic. Likewise, the age of onset of the chief complaint, as given, falls in a later decade than was the case with the uncomplicated endocrinopathies. The significant data are collected in Table X.

TABLE X.

	AGE	
Decade	Age of Admission	Onset
11-20 years	1	2
21-30 years	0	5
31-40 years	6	7
41-50 years	8	5
51-60 years	5	2
61-70 years	1	0

The first is a dependable datum, but the second is largely influenced by subjective factors that cannot be evaluated.

The average duration of the chief complaint in the group is ten years, a value, as will be shown in a later table (XIII), exceeding the dates of the thyroidectomies but falling short of those of the castrations. The chief complaints are varied and in most of the cases more than one is presented.

Fatigue in this group, as in those of the uncomplicated endocrinopathies, is a major symptom. Half presented it as a chief complaint, and practically all of the remainder mentioned it as a secondary disability.

Pain appeared as a major ailment in one-third, and as a contributory factor in practically all of the remaining cases. It

was rarely confined to a single area. The frequent incidence of pain as a symptom has already been noted in the Gonad paper, and it must be remembered that two-thirds of this group had been castrated.

TABLE XI

CHIEF COMPLAINTS

Fatigue	11
Pain	7
Obesity	4
Headache	4
"Nervousness"	4
Dyspnoea	3
Anaesthesias / Paraesthesias	3
Skin Eruptions	3
Deafness	2
Digestive Disorders	2

Four patients complained of obesity and two more exhibited it in a marked degree. In view of the usual association of obesity with endocrine failure, an analysis of this group is interesting.

TABLE XII.

OBESITY

Group	Obese > +15%	Normal +15% to —10%	Thin <—10%
Pituitary-Thyroid	2	3	0
Pituitary-Gonad	1	4	0
Thyroid-Gonad	3	5	2
Total	6	12	2

Case B-164 has been omitted.

While the normal limits adopted are perhaps too liberal, of this group three were above, three equalled, and six were below prediction, a fact offering further emphasis on the unwisdom of assuming that endocrine failure necessarily determines overweight. The dysfunctional thyroid case might be assumed to

produce emaciation, but two of the six obese patients, a just proportion, fall in this group. Headache, unassociated with menstruation and "nervousness" were or had been common complaints. The frequency of this first symptom in the endocrinopathies has recently been stressed by Drury (9). The other complaints as offered are generally recognized as frequently associated with endocrine disease.

Four of the patients gave a family history of endocrine disorders, diabetes and thyroid disease being mentioned.

In their own histories a principal point of interest lies in the surgical events which had determined the pluriglandularity of so large a portion of the group.

TABLE XIII.

Operation	No.	Date (Average)
Thyroidectomy	4	6 years previously
Single Oöphorectomy	2	7 years previously
Double Oöphorectomy	14	12 years previously

Of the thyroid subjects, two had had more than one operation, while several of the castrates had had one ovary removed prior to a second and complete operation.

The thyroid status of the group at the time of admission showed four operated cases as noted above, fourteen with no evidence of thyroid enlargement, and three with small goiters, one in each of the three major groups.

TABLE XIV-a.

MENSTRUAL HISTORY

(a) *Onset*

Year	Number
10 years	1
11 years	3
12 years	4
13 years	5
14 years	4
15 years	2
16 years	1
17 years	1

With so general an involvement of the organs of generation, the facts of the sexual histories are very informing. Almost all of the group had passed a menopause, artificial or natural, but the previous menstrual histories can be collected for presentation.

The relative values here would compare with those of any other group selected at random. Two-thirds fall within the conventional span of 12-14 years, and but three show a really early or delayed onset. No racial influence could be traced in these latter as they were all of English birth or origin.

TABLE XIV-b.

(b) *Character*

Rhythm		Flow		
		Increased	Normal	Diminished
Irregular 8	Increased	0	2	0
	Diminished	2	1	0
	Both	1	2	0
	Total	3	5	0
Regular 13		1	11	1
	Grand Total	4	16	1

Normality of function seems to be the rule with eleven patients both regular in rhythm and normal in amount, while two more are normal in rhythm and five more in amount. Three show the conventional irregularity of thyroid disease, the others scatter with but one showing a diminished flow. This is somewhat striking in view of the large number subsequently operated upon. Apparently, cystic degeneration—a common cause for castration in this group—does not lessen the flow with the same frequency that it causes irregularity.

The reproductive power of the group is a natural sequel to the preceding.

One woman is omitted as she was married twice, conceived at least thirteen times, bore two children and had at least eleven induced abortions. The second child was delivered by Caesarian section and at this time a pan-hysterectomy was performed.

The figures given above are extremely interesting in view

of the endocrine status of the group. All of them were endocrine cases although not all were certainly pluriglandular. In a larger group (100) drawn from the gonad series, 31 per cent were sterile and 10 per cent had conceived, only to miscarry;

TABLE XV.

FERTILITY

Unmarried	5
Castrated before marriage	2
Total	7
Sterile	2
Productive	12
Total	14
Of 11 married women:	
Children	18
Miscarriages	8
Abortions (induced)	1
Tubal Pregnancies	2
Total Conceptions	29

in other words, 59 per cent only had been productive. In this group 86 per cent of the women capable of bearing children had done so, the 14 per cent sterile comparing well with the average (10-12 per cent) given by Reynolds and Macomber (10) as a fair value for unselected groups.

An inference here would be that the endocrine condition was established in most of the cases in adult years after maturation and opportunity for exercise of a normal procreative function. The previous histories and ages of onset, as given, would support this idea. Of the five subjects without surgical complication, two were unmarried, one had borne five children with one miscarriage, one had conceived but terminated the pregnancy voluntarily, and the third was a young girl, 19 years of age, who had had one miscarriage in her year of married life.

While one must be conservative in the interpretation of end results in a series of cases presenting such numerous evi-

dences of conjugate endocrine involvement, the foregoing analysis certainly does not offer a direct support to the theories of pluriglandular involvement in childhood so frequently adduced to explain developmental aberration.

One other minor point may be touched upon. In the earlier papers emphasis has been laid on the frequent incidence of tonsil involvement. In the present group six had been operated once or more, four had diseased tonsils, while eleven were normal as regards the tonsils. The percentage of positive cases here falls somewhat behind the other groups but is still at a significant level.

As was noted earlier in the paper, the very nature of the cases composing this group seriously inhibits collective presentation. We have felt it better, in the interest of our readers, to conclude the discussion with a brief protocol of the case of each of the patients here included. The limitation of space determines brevity but effort has been made to include the salient details.

Part III

Case Protocols

Group I-a. Pituitary Failure and Thyroid Failure.

Case B-37. This patient was first seen in January, 1923. She gave as her chief complaint, excessive somnolence. She had had an attack of influenza at the time of the epidemic and her seizures of "uncontrollable sleep" began shortly afterward. There was no warning of the seizure but in the midst of sewing, reading or even talking the eyes closed and to outward appearances she would lose consciousness. She maintained that she was conscious of what went on about her during these attacks. The attack usually lasted from 10 to 15 minutes, they showed no periodicity and they occurred at intervals varying from days to weeks. The patient was also extremely obese but did not offer this as a complaint. Her previous hospital examination elsewhere had led to a diagnosis of pituitary failure but the patient had not benefited from a brief course of treatment which had been subsequently given. The family history gave heart failure as the cause of the father's death. There were six living siblings of whom one, was a surgical castrate who had also been studied by us. Cancer was recorded in the earlier generations. The patient had had measles and chicken-pox in childhood and typhoid at the age of 34. She had had attacks of arthritis at different times during her adult life. She reported headaches only at the time of her periods and a negative gastro-intestinal and genitourinary history. Of late years she had had some dyspnoea with palpitation and also reported occasional swelling of the feet and ankles. She had matured at 13 and believed her periods to be fairly regular. At the age of 51 the menstrual function was apparently unimpaired and she had a 4-day

period shortly before entering the hospital. Her highest weight she believed to be about 250 pounds. She weighed about 240 pounds at the time of entrance. The patient was a heavy coffee drinker, when at home averaging nine or ten cups a day. The physical examination showed a well-developed but very obese woman in middle life, her obesity tending toward a girdle distribution. The head was covered with a moderate growth of coarse dark hair; elsewhere there was no excessive pilosity. The teeth were small and irregularly spaced. There was a roll of fat around the neck and no enlargement of the thyroid could be demonstrated. The breasts were very large and pendulous, the lungs and the heart, apparently normal. The abdomen was very obese which prevented an entirely satisfactory examination. There were numerous varicose veins on the lower extremities and a small tumor growth in the lateral aspect of the right knee just outside of the patella. The knee jerks were somewhat sluggish but equal. The urine examination showed a volume of over 2½ liters; the elimination was poor, balance fair. Albumin was reported but no other abnormalities. The sediment was normal. The protein intake as gauged by the nitrogen elimination was ample and the partition formula of the latter within normal limits. The blood showed a high haemoglobin and red count, a marked lymphocytosis (60 per cent) and was otherwise normal. Chemically the blood showed an absolutely high uric acid and a slightly high blood sugar, the latter probably due to an emotional response as the venipuncture was difficult and painful. The alveolar carbon dioxide was a high normal. The serological tests were negative. The sugar tolerance was increased 50 per cent above prediction, a dose of 60 grams of galactose being necessary to produce a positive response in the urine. The patient was 81 per cent above her predicted weight, while the lung capacity was less than half that predicted by the Dreyer standard. The basal rate was —34 per cent, the pulse and temperature being substantially normal, the blood pressure relatively somewhat low. A neurological examination gave substantially normal findings. It gave no evidence of organic lesion. The patient was somewhat dull mentally without exhibiting any psychotic element of significance. The eye examination showed normal fields, blind spots slightly enlarged and apparently normal discs. A radiogram of the aortic arch showed a thickened wall. The remaining chest X-ray findings were normal as were those of the skull, sella and sinuses.

Discussion: The picture presented by this patient was clearly endocrine but the actual gland or glands at fault were not easy of determination. The large volume of the urine, the high blood uric acid, normal nitrogen partition, the somewhat low blood pressure, normal pulse rate, 'phthalein test, and relatively large increase in the tolerance threshold were all suggestive of pituitary deficiency. In addition, the type of distribution of her obesity, the history of her presenting difficulty, and a number of other points elicited in the physical examination and history were confirmatory. On the other hand, the magnitude of the deviation of the basal rate was greater than we have ever associated with uncomplicated pituitary failure. The lack of excessive hair growth and other points of a like nature, tended to emphasize the thyroid element. At the time of the examination it was felt that this case might properly be classed as a true pluriglandular condition with lowered functional activity both of the pituitary and the thyroid. That a therapeutic test might be given, the patient was placed on thyroid medication alone with observations made at fairly frequent intervals. The basal rate improved somewhat, reaching in mid-June a level of —19 per cent. The

weight was unchanged, the pulse remained in the mid-seventies, and there was no effect on the sugar tolerance. The thyroid dosage at this time was somewhat variable as the patient's cooperation was not complete. Her average intake, however, was of the order of 5 or 6 grains per day. Pituitary medication was added to her variable thyroid intake and in October of the same year (1923) a partial study was made. The urine volume had dropped somewhat but was still ample, averaging about 1800 c.c. Albumin persisted. The earlier normal residual nitrogen remained unchanged. The earlier lymphocytosis was at the same high level. Body weight had decreased but three kgm., and practically all of the other findings were at the earlier level. Two changes, however, were recorded. The basal rate had become normal and the sugar tolerance had dropped to 50 grams. The patient was discharged with the recommendation to continue both the thyroid and the pituitary treatment and was seen again in March of 1924. There was reason to believe that again she had not been consistent in following her treatment but equally that she had taken a good deal both of thyroid and of pituitary substances. The urine presented the same general picture as did the blood chemistry and blood morphology. The patient had lost some 10 kilograms more but was still markedly obese. The basal rate at the time of the study was —12 per cent with a pulse of 70. The "sugar tolerance" could not be secured.

This patient represents one of the few cases in our very long series in which, seemingly, there was simultaneous primary involvement of two endocrine glands. On thyroid medication alone the patient showed but little change, while her history showed that her earlier pituitary medication had been equally ineffective. The combination of the two was apparently necessary to normalize the basal rate and induce such changes as were recorded. Her attacks of drowsiness had become less during the fifteen months but as they had been showing a lengthening interval before we studied the case, it is not legitimate to ascribe this improvement certainly to the medication. The patient's relatively slight loss of weight was undoubtedly ascribable to her unwillingness to curb her large appetite. She was studied early in the present series of investigations. Certain laboratory procedures which have since become available and, more importantly, a number of skilled opinions in the specialized fields of medicine were not available at the time of this study. Shortly after the last observation in 1924 the patient moved to the far West and we have had no further news of her since that time. From the data available, recognizing its incompleteness, we feel constrained to report this patient as presenting a genuine pluriglandular condition.

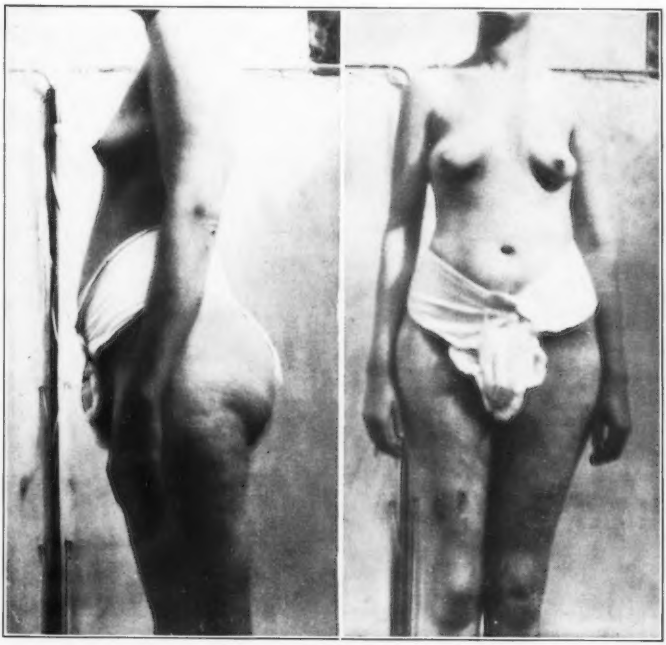
GROUP I-b. PITUITARY DYSFUNCTION WITH THYROID FAILURE.

CASE B-18. This patient was admitted in 1922 for a study of her endocrine status. She was a woman of 35, nearly 6 feet 3 inches tall, who complained of an anaesthesia of the middle third of the body accompanied by incontinence of bladder and rectum. Three years previously she had been admitted for retention of urine and the use of the cystoscope revealed her anaesthesia in this region. Under treatment the condition cleared up in about 3½ months. When readmitted in 1922 for this study, she stated that she had been unconscious of the passage of feces since her illness three years before, and that a similar condition existed in regard to urination. It seemed probable that some degree of the anaesthesia of the anterior

portions was of much longer duration, since she had never been conscious of the menstrual flow escaping from the vagina. There had never been any sex urge.

A second complaint was recorded, namely, back pain, from which she had suffered for about 10 years although she gave a history of weak back from the age of 10. She had been under orthopedic care and had worn various supporting appliances, from which she derived some benefit, for a number of years.

PLATE I



CASE B-18

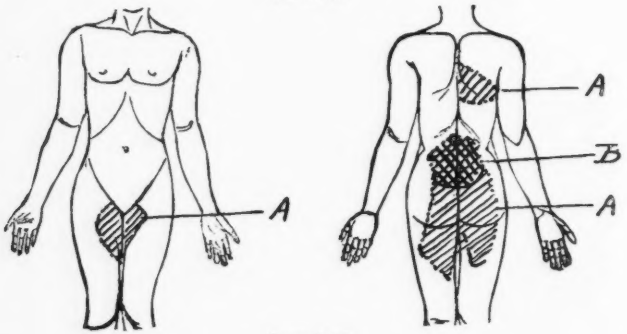
Both parents had died of diabetes and both were extremely obese, the father weighing 300 pounds and the mother 275 pounds. Her only sibling, a brother, had been 6 feet 4 inches tall and had recently died of advanced nephritis. The patient's own history included minor ailments and scarlet fever previous to her eighth year, at which time she had a severe attack of chorea, following which she had had to learn to walk again. Between the ages of 10 and 12 she grew to her present stature. The menses had been established at 13, and showed a somewhat shortened regular interval and scanty flow. The mental development had been wholly normal. The physical examination showed a very tall girl with low sitting height index

(0.50) and a tendency to girdle obesity not shown in other parts of the body which were somewhat underweight (see Plate). The head and body hair was somewhat scanty and of normal distribution. The thyroid was somewhat enlarged, the chest and abdomen normal. Rectal and vaginal findings were normal except for the anaesthesia. An earlier radiogram of the spine had shown no spina bifida; a very complete series of plates of the entire body showed no pathological changes in either the bony structure or the viscera. The neurological findings will be discussed in detail elsewhere. Summarized: three years previously, the tendon reflexes had been reported as normal; at the time of this examination the Achilles and knee jerks were absent. The anaesthetic areas are shown in the accompanying chart (q. v.).

The urine volumes were normal, elimination and balance good. Albumin was present; the remaining findings, including the nitrogen partition, were normal. The blood morphology was normal, the blood chemistry equally so, and the serological tests were negative. The 'phthalein elimination and CO_2 level were normal. The sugar tolerance was slightly depressed, the "vital capacity" comparisons substantially normal. (The low sitting height index has already been noted.) A series of basal rate determinations gave values between —20 per cent and —25 per cent with definitely low blood pressure and slow pulse. A urea curve was normal.

Discussion: With the patient's bodily habitus and history, the first thought here would be of an earlier over-active pituitary pass-

PLATE II



CASE B-18

ing through a functional involution state and presenting the common dysfunctional formula. The sugar tolerance would harmonize with this idea, as would the observed level of the basal rate. The eosinophilia and high blood uric acid are lacking, and the blood pressure, pulse rate and alveolar CO_2 are at levels more suggestive of thyroid failure. The observed basal rates were as low as —25 per cent, a somewhat extreme value for anterior lobe failure—and it was questionable if the patient were ever in a truly basal condition. The thyroid enlargement was not necessarily meaningful as it is a not infrequent report in cases of uncomplicated pituitary disease, to say nothing of its frequency in normal and non-endocrine conditions. In other words, there were evidences of a possible true pluriglandular

state in which the pituitary was the earlier and recessive, and the thyroid failure, the later and dominant element. On this basis a tentative diagnosis was offered and thyroid medication instituted. The anaesthesia gradually cleared up and the incontinence disappeared. This response to the thyroid medication is felt to offer some support to the initial diagnosis. The later history of this subject will be reported later; none of its events have thrown any more light on the basic, underlying endocrinopathy. In fairness, we feel that it must be reported as a pluriglandular involvement, although the pituitary element was principally represented by structural residua.

CASE B-532. The patient was a woman of 33 referred to this Clinic primarily for obesity. She had been married for 10 years during which time she has six pregnancies, the first resulting in a miscarriage at three months and the other five in viable children three of whom, however, showed a definite retardation in mental development. At the time of her marriage the patient was not strikingly obese. After this event, however, she began to increase weight, and after the completion of her fourth pregnancy she weighed 160 pounds. She then began to gain more rapidly and in the course of 5 years reached nearly 250 pounds. By rigorous dieting she reduced herself about 40 pounds in the course of a year, but prior to admission had begun to gain again and weighed 215 pounds when we first saw her. Both of her parents were said to be extremely nervous. She had two brothers who were well and apparently normal. She reported one aunt who was a diabetic and extremely obese. Of her own history she reported the usual minor ailments of childhood together with scarlet fever, influenza at the time of the epidemic, and pneumonia in 1922. A breast abscess was lanced in 1917. She had occasional headaches when fatigued and what she described as neuralgic headaches when her teeth were in poor condition. This latter condition was seemingly one of recurrence and there was a long history of dental troubles. She complained of vertigo during her pregnancies. Within the past three years there has been much thinning of the hair on the vertex. She noted optic fatigue, some loss of hearing, frequent severe attacks of rhinitis and, she believed, some nasal obstruction. The cardiac history was substantially normal. She had been fatigable for a number of years and this condition was accentuated during her pregnancies. After each confinement there was a brief period when the patient had night sweats. Experience had shown that unless food were taken shortly after arising there was a tendency to nausea. The periods began at 13, were regular, and apparently normal in amount. She had had recurrent attacks of pimples on the breasts. For many years she had had some intermittent pain in the legs and knees. There was also stiffness of the neck, and at the time of the breast abscess there was "articular rheumatism" in all the joints. Of later years she had experienced numbness and cramps in the legs and tingling in the hands associated with coldness of all extremities. There had never been any evidence of mental impairment, she having made excellent records at school and college. The physical examination showed a definitely obese woman with a marked tendency toward girdle distribution. The eyes and ears were normal, the tonsils slightly enlarged and cryptic, teeth in poor condition, no apparent thyroid enlargement, heart and lungs normal, abdomen markedly obese, arms and legs large, ankles possibly slightly edematous; the hands, wrists and feet were small. There was a slight scoliosis, a slight cervical adenopathy; the skin was somewhat hypertrophic and dry. Routine neurological findings were normal. The urine was normal in amount;

elimination and balance were poor. One specimen showed albumin and all, a trace of sugar; the sediments were normal. The nitrogen partition determination showed an elimination indicating a somewhat low protein intake; the partition formula was normal. The blood showed a marked relative lymphocytosis (47 per cent) and a 3½ eosinophilia. The blood uric acid was above the normal level, the blood sugar normal. The serological findings were normal. The 'phthalein elimination was somewhat low. The patient's sugar tolerance was half the level normal for a woman of her age and sexual status. By the Dreyer standard she was 38 per cent overweight, but her obesity was actually in excess of this as the sitting height index was 0.55, a value well above the normal. Her lung capacity was slightly above prediction. Two independent basal rate measurements gave a value of 44 per cent below prediction, with slow pulse and a blood pressure just below 100. Her alveolar CO_2 was normal. X-ray findings of the heart, lungs and mediastinum were all normal; of the teeth showed much alveolar absorption and several periapical abscesses. A neurological examination gave no postive neurological findings. A nose and throat examination demonstrated a slight septum deviation not sufficiently important to warrant interference. A cardiogram showed a slight sinus arrhythmia and low voltage but was otherwise normal; this finding was confirmed by a heart consultation. The eye grounds showed yellowish discs, enlarged blind spots, and some symmetrical contraction of the form and color fields.

Discussion: The majority of the findings in this case were entirely harmonious with the general picture presented by a case of pituitary dysfunction. The normal urine volume, slight glycosuria, the normal nitrogen partition formula, the slight eosinophilia, high blood uric acid, lowered galactose tolerance, normal lung capacity, high alveolar carbon dioxide, integrate to form a picture of pituitary disease. This conclusion is supported by a number of points in the history and physical examination. On the other hand, the basal rate was at a level which had been observed by us only in thyroid failure; with this was a blood pressure definitely lower than that usually recorded in pituitary disease, and also a slow pulse. A urea curve showed a normal shape with somewhat depressed elimination, and the 'phthalein test was somewhat low—factors again more suggestive of thyroid failure. Here again the various data, while defining unmistakably an endocrine disturbance, exhibit magnitudes and directional relationships which it would be difficult to associate with the uncomplicated failure of a single gland. The patient was put on thyroid medication. Four months later she had lost less than 2 kilograms, exhibited an unchanged blood pressure and pulse rate, and a basal rate still 27 per cent below prediction. Thyroid medication alone was continued for three more months without producing any change, the patient gaining 0.2 kgm. in weight and showing a basal rate of —23 per cent. Pituitary medication was then added to the thyroid and later reports show a definite improvement, although we have no laboratory records of later basal rate measurements.

This case like that of B-37 is seemingly one of simultaneous involvement of both pituitary and thyroid. The pituitary formula is not the same, as in this case the posterior lobe exhibits a definite overactivity, while in the first a bilobar failure was the condition. With the data available and such knowledge as we possess of endocrine disease at this time, diagnosis of a pluriglandular condition involv-

ing both the thyroid and the pituitary is seemingly the only one which is warranted.

GROUP I-c. PITUITARY DYSFUNCTION WITH THYROID DYSFUNCTION.

CASE B-141. The patient's chief complaint was of a steady increase in weight coupled with an increasing dryness of the skin and an intermittent flushing of the chin, cheeks and upper chest. Some 17 years previously the patient began to develope a disturbing nervousness and to lose weight. This condition continued progressively until 1911 when a diagnosis of hyperthyroidism was made and an operation performed. Two years later there was some recurrence of the earlier symptoms and on her own initiative the patient instituted a course of thyroid medication. Somewhat later this procedure was approved by her physician. The thyroid therapy was subsequently discontinued and a year before the patient was admitted to this Clinic she began to develop the symptoms which ultimately led to her reference here. She was a woman well above the average height; one of her siblings was 6 feet 4 inches tall at the age of 14 and was mentally deficient. The father had diabetes for a long time prior to his death; the mother had had Graves' disease, was operated upon and developed myxedema before her death from heart failure. Eight siblings were alive and well. The patient's own history showed only the minor ailments of childhood outside of the events recorded above. She had been married for 21 years. Her first pregnancy terminated in a miscarriage. Subsequent examination disclosed a retroversion of the uterus for which the patient was operated upon. A second pregnancy terminated at full term but the child was stillborn, delivery being instrumental. A third pregnancy resulted in a viable child which died, however, two years later of meningitis. The fourth and last pregnancy ended in a miscarriage at three months. The patient matured at the age of 10 and the menstrual function was normal and regular up to that of 15. During this interval she grew very rapidly and at the age of 14 was 5 feet 11 inches tall and weighed 170 pounds. From 15 years of age, to the time of her marriage her periods came every two weeks and were very copious. With marriage, the interval and amount again normalized. When seen by us at the age of 51 she had just passed an uneventful menopause. The patient gave a history of severe headache with her pregnancies and during her attacks of hyperthyroidism. She was at no time fatigable—in fact mentally and physically she was distinctly above the average. She had diarrhoea in the summer time but was never constipated. The remaining history was not remarkable. Physical examination showed a tall woman with high color, not excessively overweight. The bridge of the nose was underdeveloped: the teeth showed some dental attention, there was a slight residual thyroid enlargement, heart and lungs were normal as were the routine neurological findings. The skin on the lower part of the body was dry and scaly. The urine volume was normal, elimination and balance good; a small amount of sugar and increased indican were reported. The sediment was not suggestive. The nitrogen partition contained a high residual fraction. The blood showed a definite lymphocytosis but was otherwise normal. The serological tests were negative. Blood chemistry was normal; the 'phthalein test somewhat low. The patient had a greatly depressed sugar tolerance, a dose of 5 grams of galactose per os being sufficient to produce a trace of galactose in the urine. She was 14 per cent overweight and had a normal sitting height index. The lung volume was 25 per cent below prediction. Alveolar carbon

dioxide was slightly low. The basal rate was —6 per cent with a somewhat hypertensive level of the blood pressure and slightly slow pulse. The eye findings were substantially normal; examination of the fundus showed some vascular sclerosis. The pelvic examination demonstrated residua of her earlier childbearing but was otherwise normal. Radiography showed the skull and sella to be normal; the aortic arch was prominent; otherwise the chest was apparently normal.

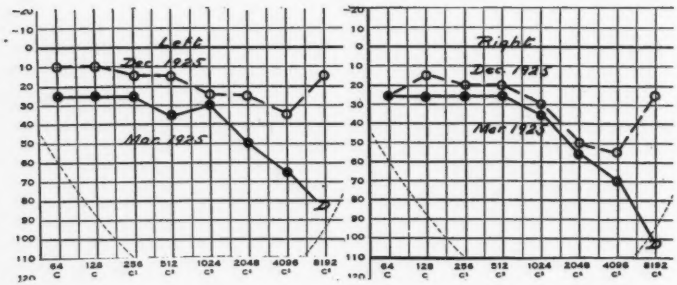
Discussion: While a complete resolution of this case involves a certain amount of speculation and surmise, certain points would seem to be fairly established. That the patient presented a pituitary aberration in adolescence, there can be but little question. A residuum of the posterior lobe overactivity is manifest in the very low galactose tolerance threshold. Her relatively normal basal rate must be regarded as due to the sum of the thyroid and pituitary influences. That there was an earlier thyroid overactivity must, we believe, be accepted. The operation had unquestionably lowered this activity but to what extent, it can not with certainty be said. If the pituitary disease had terminated in the usual dysfunctional formula, then the anterior lobe would be below a normal level, and this could be compensated by a residual slight overactivity of the thyroid. But it must be remembered in interpretating all basal rates that the values observed are maxima and that the true basal rate may well be definitely below that observed. The patient was an extremely intelligent woman with a sound philosophy of life. In spite of her previous medical contacts which had involved basal rate determinations she was a little nervous although controlled at the time of this test. As we saw this case a probable earlier hyperactive pituitary had in part undergone a functional involution, leaving a characteristic dysfunctional formula. Superimposed upon, and independent of, the pituitary condition a possible hyperthyroid activity had supervened. Operation had produced a dysthyroidism of relatively minor moment. If there were aberrant thyroid activity it would presumptively be on the side of some residual hyperfunction—at least of that element in the gland which influences oxygen requirement. Obviously, medication for such a condition must stress the potential pituitary state and ignore the probably less significant thyroid. There is certainly no evidence presented that would warrant further thyroid operation. On this basis anterior lobe medication was recommended and subsequent reports both from the patient and from her referring physician recorded a marked general improvement. This case presents a type of pluriglandularity in which one endocrinopathy is superimposed upon a second which had antedated it, usually by a considerable interval. The general picture, here, in the main reflected the dominant and initial endocrine disturbance. The thyroid element was an added effect, was not adequate to produce marked changes in the disease picture engendered by the primary endocrinopathy, and in its present status derived, in some measure at least, from the earlier surgical intervention. A possible alternative explanation would have been a thyroid failure of surgical origin complicating a still earlier existing bilobar hyperpituitary activity. Had this been the case the exhibition of anterior lobe medication would presumably have produced unfavorable results on the patient's symptoms. The marked betterment which she reported leads us to feel that the first hypothesis discussed offers the larger measure of probability.

CASE S-568. This patient was referred to us for deafness, of which she had been conscious for the past 3 or 4 years. The progress had been gradual and the severity somewhat variable and influenced by the patient's nervous condition. She had not experienced tinnitus nor did she show paracusis. Some years prior to her recognition of the condition she had been under a severe nervous strain and she felt that this, in part, might have been operative in determining the condition. A brother and an uncle were both deaf. She reported several cases of cardio-renal disease in near relatives. The patient's own history showed the usual minor ailments of childhood, as well as diphtheria and scarlet fever. She had the influenza in 1918 and several attacks of tonsillitis prior to a "T. & A." operation three years previously. She was occasionally constipated and when in this condition she developed nausea and vomiting. The menstrual history showed a normal onset and an uneventful history including the menopause which latter had transpired some two years before. She had been married for 7 years with one pregnancy ending in an induced abortion. She complained of dizzy spells which came at irregular intervals. The condition would last for a month or two and then she would be free for perhaps a year. Her social history included several events calculated to produce a marked degree of nervous tension. The patient was nervously unstable and markedly fatigable. A study carried out some time previous to her entry into this Clinic defined her deafness as of a toxic type and assigned the teeth, gastro-intestinal tract and, at the time of that examination, the menopause, as contributory factors. Prior to her admission the patient had experimented with small doses of thyroid and of ovarian preparation without noticeable benefit. Physical examination showed a well developed, slightly obese woman, of 55; there was a suggestion of exophthalmos and a slight edematous pouching beneath the eyes: several teeth were missing, and the remainder showed much dental attention. There was a slight struma, a slight pleuritic rub was heard in the right chest, the heart and abdomen were normal, and skin on the extremities dry and scaly. The fat distribution suggested the girdle type. The hair distribution was normal. The urine showed a normal volume, good elimination and poor balance; a trace of sugar was reported; the sediment was normal. The nitrogen partition implied an inadequate protein intake and gave a high residual nitrogen. The blood showed a somewhat low haemoglobin, a slight leukopenia, a relative increase in the lymphocytes, and a 5 per cent eosinophilia. The blood was normal in chemical composition with the uric acid relatively high. The serological tests were negative. The phthalein output and alveolar carbon dioxide were normal. She was 12 per cent overweight and nearly 30 per cent below her predicted lung volume. A fairly satisfactory basal test gave —25 per cent, a somewhat rapid pulse and normal blood pressure. The radiographic plates showed a large sella, 16 mm. x 15 mm., and a negative chest and skull. The eye examination disclosed yellowish discs, slightly enlarged blind spots, and a very slight cutting of the form field. The audiogram, herewith reproduced, showed a marked loss of hearing in the upper tones in both ears, and some diminution in the lower register. The cardiogram was normal.

Discussion: The case presented several points of interest. In the first place the rapid pulse, low basal rate—for the value recorded was undoubtedly above the truth—enlarged thyroid and suggestion of exophthalmos were suggestive of a thyroid failure. Equally, the lowered sugar tolerance, eosinophilia, eye findings and enlarged sella

were more in conformity with a pituitary condition. We felt that the inconsistency between the sugar tolerance and the magnitude of the basal rate could best be explained by the assumption of the existence of a true pluriglandular condition. Analysis of the entire case, however, with proper weighting of the several differential factors led to the conclusion that the pituitary influence at the time of the examination was distinctly less than that of the thyroid. On this basis it seemed desirable to attempt a therapeutic test with thyroid medication alone, and with the patient's consent this was done. The results of this treatment, which had been carried on since that time, had, in the main, been very satisfactory. The patient's hearing, as shown by the audiograms and by clinical tests, has definitely improved. A considerable amount of nervous instability has disappeared, and from the clinical standpoint there has been a definite and unmistakable improvement. It has been found expedient

PLATE III



CASE S-568

in this case to supplement the thyroid extract with some thyroxin and she has also received courses of treatment with anterior pituitary. These latter, however, have been of brief duration and we are uncertain if this latter medication has played any real part in the patient's betterment. We have recorded the case but without marked enthusiasm as one of pluriglandular involvement. It is possible that this case is essentially one of thyroid dysfunction and that the pituitary evidences were apparent rather than real.

Many of the data suggesting a pituitary involvement could equally derive from a diseased thyroid in a transition state between an initial hyper- and final hypo-activity. As was noted in our earlier paper on the thyroid (3), patients presenting this condition are not uncommon. Another possible explanation of the lowered sugar tolerance and other pituitary evidences could lie in the existence of a low-grade liver dysfunction, a condition of which certain portions of the patient's history are suggestive. While we feel that the diagnosis of uncomplicated thyroid dysfunction holds the largest measure of probability, the data as presented, in fairness warrant the tentative inclusion of this case in the pluriglandular group.

GROUP IIa. PITUITARY FAILURE AND OVARIAN FAILURE.

CASE B-659. This patient was referred for a group of symptoms including dizziness, numbness of the hands, dyspnoea, palpitation, and

pain in the left costal border. She was a woman 65 years of age who, at the age of 35, had had one ovary removed and at the age of 50, the uterus and remaining ovary. Seven years prior to admission, the patient then being 57, she developed intermittent attacks of numbness and tingling in the hands. Various treatments were tried but without success. During substantially the same interval she had had pain along the left costal border which was also intermittent. Dizziness, palpitation and dyspnoea had been of but one year's duration. There was a familial history of tuberculosis and of cardio-renal disease. During the patient's 13 years of married life she had never conceived although contraception was not practiced. For the 34 years preceding her admission she had worked very hard. She reported all of the minor ailments, together with diphtheria, scarlet fever, tonsillitis, and pleurisy. She recounted only the two operations noted above. Recently she had developed headaches but for many years had been troubled with pain and lacrimation in both eyes, coupled with failing vision. She was deaf in the left ear and often had pain in the right. Most of her teeth had been removed. She was markedly constipated; there was some nocturia. From her history, although her statements were not completely informative, it seemed probable that her husband had infected her with gonorrhea during her married life. The menses were established at the age of 11; the periods were regular but were always scanty. An uneventful menopause antedated her hysterectomy by five years. During the last few years she reported a steady increase in weight. Physical examination showed an obese woman in the mid-sixties, with a moderate amount of grayish-white hair, that on the body being normally distributed. The features were full and coarse. The left ear was practically deaf. There was slight hearing power in the right. The few remaining teeth were in fair condition. The thyroid was not enlarged. Heart, lungs and abdomen were substantially negative. The peripheral vessels gave some evidence of arteriosclerosis. The routine neurological findings were normal. The urines were normal in volume, the elimination good, the balance poor. One specimen showed albumin and all sediments showed much epithelial debris, but no casts were observed. The protein intake was barely at a maintenance level. The residual nitrogen fraction was high. The blood showed a slight leucocytosis with increase in the lymphocytes, while the oesinophiles were normal. The blood showed chemically, a slight upward tendency in all of the nitrogenous constituents. The serological tests were negative. The 'phthalein output was low. Galactose tolerance was 200 per cent above the patient's predicted normal. She was 52 per cent overweight and the lung volume was depressed about 40 per cent. The basal rate was —20 per cent in several concordant tests; her blood pressure was at the hypertensive level of 170/100. The pulse rates were in the lower sixties. The urea curve showed a fairly normal elimination. The alveolar carbon dioxide was normal. The radiographic study of the skull and chest was normal. A neurological report commented on the paraesthesias as reported coupled with the absence of any objective findings of significance. The heart examination determined an organ normal for her age and a tolerance for exercise reasonable for her weight. In the examiner's opinion there was no evidence of angina and he felt that the pain of which the patient complained might be due to mechanical causes connected with the lax and obese tissues. An audiogram showed marked but not complete loss of hearing in both ears. A Barany test gave normal responses. Pass pointing was within normal limits. The eye examination

showed contraction of the form and color fields to about 30°. The discs were yellow, the left blind spot enlarged and in the right eye a scotoma was demonstrated signifying involvement of the paramacula fibers.

Discussion: The patient's non-endocrine disease, consisting of her arteriosclerosis, hypertension, and early nephritis, obscures certain of the features of the general picture. The patient's history of surgery emphasizes one definite endocrine failure, while the laboratory findings indicate as well the presence of a bilobar pituitary failure. At the patient's age and with the non-endocrine elements in the case but little could be hoped from endocrine medication. Whole pituitary was recommended but contact was lost and we are not informed of the outcome with the case.

CASE S-744. This patient was a woman of 45 who was referred to the Clinic, presenting a progressive impairment of vision and a rapid decay of the teeth as her chief complaints. In regard to the first, she stated that she had worn glasses for 16 years, but during the last 3 or 4 years the vision had deteriorated rapidly. For many years she had been troubled with headache, which was usually frontal in character, although it occasionally involved the occipital region. These headaches occurred several times a week and were seriously disturbing. The patient had been married for 19 years, and during this time she had had five pregnancies resulting in three viable children and two miscarriages. Following the birth of the last child the teeth began to deteriorate. Six years ago both ovaries had been removed. The family history showed that the mother suffered from similar headaches; the father was diabetic and, of two living siblings, one was a chronic invalid. Three brothers and one sister had died before the age of one year. The patient's own history showed only measles in childhood, a sinus operation, an appendectomy at the time of her castration, and a dilatation and curettage after each of her miscarriages. She had been in an automobile accident eight years previously and had lost consciousness for a few moments. She was not aware, however, of any subsequent ill effects. She stated that at the age of four years she had been blind for several weeks. She was ignorant of the cause of this condition, which apparently corrected itself spontaneously. She complained of occasional tinnitus, with no loss of hearing, constipation and a susceptibility to head-colds. The catamenia was established at the age of 15; the periods had always been irregular with increase in the interval, and the flow was scanty. Physical examination showed a small woman (5 feet), well developed and slightly over weight; the hair was coarse and slightly gray; body hair distribution normal. There was a slight divergent strabismus, the teeth showed much dental attention, the pulse rate was slow, and the remaining report, including the routine neurological examination, was not suggestive. The urine volume was normal, the elimination and balance good. The urinary nitrogen partition showed a somewhat low protein intake and a normal formula. She had had a slight secondary anaemia and a lymphoid blood with slight increase in the eosinophiles. The blood chemistry and phthalein test were normal. The serological tests were negative. The alveolar carbon dioxide was slightly below the normal. The patient was 12 per cent overweight and her lung volume was slightly below prediction. The basal rate was —23 per cent; there was some lowering in pulse, blood pressure, and body temperature. The sugar tolerance was 50 per cent above her predicted level. Radiograph of the skull

showed a small, shallow and flattened sella. An eye examination showed yellowish discs and enlarged blind spots.

Discussion: To evaluate this case, it is, of course, essential to make allowance for the effect of her surgical hypogonadism. On this basis she presents evidences of a bilobar pituitary failure, which, added to the endocrine effect of her castration, determines a technical pluriglandular condition. Pituitary medication (whole gland) was advised.

CASE S-1327. The patient's chief complaint was of a skin eruption, from which she had suffered for several years. She also complained of severe headaches and a blurring of vision which followed spells of numbness on the left side. The patient had been married for 8 years and 3 years after marriage a tubal pregnancy necessitated the removal of one tube and the ovary on that side. Two years later an ovarian cyst was resected, and again 2 years after this the ovarian remnant and the uterus were removed. The skin eruption followed the first laparotomy, first showing as groups of small postules. For the preceding six months it had become more severe. Twenty-four years before, at the age of 11, the patient began to have spells of numbness, usually following violent exercise. At the same time a lateral hemianopsia developed, lasting for about fifteen minutes. The numbness would spread following this and last perhaps three-quarters of an hour and disappear spontaneously, leaving a severe headache as a residuum. Latterly, the spells of numbness had been confined to the left hand and left side of the body. These attacks at the time of admission were occurring at intervals of from a few weeks to several months. During them the patient never lost consciousness nor fell. The family history showed cardiac disease on the paternal side and was otherwise not significant. The patient had had various minor ailments and the influenza in 1918. She complained of occasional attacks of vertigo, some gastro-intestinal disturbance, urinary frequency during the day, and some nocturia. The catamenia was established at 13 and the history was not remarkable prior to her artificial menopause. The physical examination showed a well developed and well nourished woman in her mid-thirties. The eyes were normal, the teeth showed much dental attention, the tonsils were the seat of chronic inflammation and the anterior pillars were slightly injected. The thyroid gland was slightly enlarged. The heart showed a slight systolic murmur at the apex; there was a definite right scoliosis in the lower dorsal and upper lumbar region and marked prominence of the upper lumbar vertebrae. Some resistance and tenderness were found in the lower left quadrant. Note was made of the skin eruption confined to the chin and right cheek. The urine volumes were normal, elimination and balance good. One specimen showed a very slight trace of albumin. The nitrogen partition was normal. The blood showed a slightly low haemoglobin and a slight leucocytosis, the increase occurring in the neutrophilic elements. The blood showed chemically a relatively high uric acid. The serological tests were negative. The phthalein output was normal and the alveolar CO_2 was low. The patient was 5 per cent below her predicted weight and had somewhat less than her calculated lung volume. The basal rate was observed as 15 per cent below prediction, the true rate being probably somewhat lower, as the patient was slightly nervous; earlier and less satisfactory tests had given —6 per cent and —10 per cent, respectively. The pulse was normal and the blood pressure low. An orthopedic examination defined the scoliosis as deriving from faulty

posture and of no real significance. A neurological examination failed to find evidence of organic nerve disease and the history was regarded as suggestive of migraine, as both transient palsies and hemianopsia may be associated with this condition. Endermal tests gave only negative response to a large number of food proteins. The patient's sugar tolerance was 50 per cent above prediction. A heart examination gave no evidence of disease and a cardiogram confirmed this opinion. X-ray studies of the sella, skull and sinuses were normal, as were those of the spine, pelvis and hips. The eye examination showed yellowish discs, enlarged blind spots and a possible slight contraction of the form fields. A dermatological examination defined the presenting condition as rosacea.

Discussion: In the evaluation of this case it is essential to remember that the patient has a definite endocrine condition of surgical origin, which inevitably influences certain of the results. For example, the low alveolar carbon dioxide and the low blood pressure should be ascribed to the hypogonad condition. With so relatively slight a drop in the basal rate, even though the true basal were not obtained, one would not normally trace a thyroid influence, certainly not one of a magnitude to produce the definitely increased sugar tolerance which in our experience is only found in profound changes of thyroid activity. The bulk of the evidence was felt to point to a bilobar pituitary failure, and this, with the patient's surgical hypogonadism, defined a pluriglandular condition. Whole pituitary medication was recommended and reports from the referring physician record a marked improvement in the patient's general picture and at the end of three months a practically complete disappearance of the skin eruption.

CASE S-1343. The patient's chief complaint, as offered by herself, was a susceptibility to infections of the respiratory tract coupled with asthma. During the past year she has been extremely fatigable and has felt that her resistance was particularly low. She ascribed this to her repiratory difficulty. During the preceding winter she had a heavy cold and a severe, persistent, productive cough. The family history was not significant beyond a record of longevity in the older generations. The patient had been married for 23 years and had borne two children without a miscarriage. Six years before admission the ovaries and uterus had been removed. She stated that she was a delicate child and had never been rugged. The history included a few minor ailments and an appendectomy 20 years before. She had hay-fever every June. She had been treated with serum for her asthmatic attacks with apparently excellent results. The catamenia was established at 14 and the menstrual history was normal up to the time of her pan-hysterectomy. Physical examination showed a fairly developed and well nourished woman in the late forties. The hair was gray and abundant. The tonsils were enlarged and inflamed. The patient stated that she had had bad tonsils for a long time, but had been advised against operation. The chest showed some dulness, scattered rales and somewhat increased focal fremitus. The heart showed a soft systolic murmur, apparently not transmitted. There was a slight mass in the right lower quadrant which the examiner ascribed to adhesions. From the patient's history as given, the appendiceal condition was bad at the time of her operation. The residual examination was not significant, including the routine neurological study. The urine volume was well in excess of two liters, the elimination good, but the balance poor; is otherwise

normal. The nitrogen partition showed a low, but adequate, protein intake with a markedly high residual fraction. The blood morphology was substantially normal except for a 14 per cent eosinophilia which was ascribed to the hay-fever and asthmatic condition recorded in the history. The blood uric acid was high. The phthalein test, alveolar CO_2 tension and vital capacity comparisons were all normal. The serological tests were negative. An unsatisfactory basal rate gave a level of —7 per cent. The true rate was certainly lower, although how much it would be impossible to say. The patient declined to repeat the test. She showed a hypertensive blood pressure and a somewhat slow pulse. Radiography showed the sella to be large and recorded a thinning of the wall of the posterior clinoid, presenting a picture suggestive of an hypophyseal tumor. The sinuses were normal, as was the chest. The eye examination showed moderate vascular sclerosis and yellowish discs; the right blind spot was slightly enlarged and there was a suggestion of cutting in the right form field. The patient's sugar tolerance was 100 per cent above prediction.

Discussion: The patient's clinical history determined ovarian failure. Superimposed upon this was an undoubted pituitary involvement. With the marked increase in the sugar tolerance and the presumptively lowered basal rate this latter condition would be a bilobar pituitary failure. The roentgenograms gave some evidence of pituitary tumor. On the basis of this diagnosis the patient falls conventionally into the pluriglandular group.

CASE S-1669. The patient's chief complaint was of recurrent temporal headaches. These started in childhood, but with the onset of catamenia they increased in frequency and severity. They had been initially unilateral in onset, but would spread over the whole frontal region in their course, which was usually three to four days. Seventeen years before admission, the patient had one ovary removed, and ten years later the uterus and remaining ovary were ablated. Since this latter event the headaches had been still more exacerbated, might be accompanied by nausea and vomiting, and were associated with pronounced mental depression. In the family history were recorded similar headaches in the father and one sister, but otherwise nothing significant. The patient had had all of the minor ailments of childhood, pleurisy following tonsillitis at 12, and several later attacks of the latter until a tonsillectomy 15 years before. She had had several brief attacks of mild generalized arthritis. She had worn glasses for many years without influencing her complaint. Her appetite had been fair, with the voluntary elimination of sweet and rich foods from her dietary. She was severely constipated and had been troubled for years with hemorrhoids. The catamenia had been established at 12, was at first irregular, but after some two years became regular with somewhat shortened rhythm. The flow was normal in amount. An uneventful menopause had occurred some six months before her hysterectomy, which was for a fibroid tumor.

The physical examination showed a well-developed and nourished woman of 51, with slight pilosity on the upper lip, but other hair distribution normal. The remaining findings were completely normal. The urine volume was ample, the balance of the observations not significant, except for a high residual nitrogen fraction. The blood showed a lymphocytosis and slight (3.5 per cent) eosinophilia. The blood uric acid was relatively and absolutely high, the serological tests were negative, and the phthalein output and CO_2 level normal.

She was at her predicted weight, but appreciably below (36 per cent) her calculated lung volume. A fairly satisfactory basal rate measurement was 12 per cent below prediction, with somewhat lowered pulse and blood pressure. X-ray plates showed a large sella and obstructed nasal fossae, but otherwise normal findings. The sugar tolerance was 100 per cent above her normal level. The eye examination showed yellow discs, enlarged blind spots, and some cutting of the fields, more marked in the left eye.

Discussion: The picture given above defines a bilobar pituitary failure, with but few of the conventional evidences lacking. In addition, there is superimposed a surgical hypogonadism, making the diagnosis technically pluriglandular failure.

Group IIIa. Thyroid Failure and Gonad Failure

Case S-686. This patient was a girl of 19, who complained of frequent headaches in the frontal and supra-orbital region, from which she had suffered for about a year. A recent eye examination had failed to disclose any cause for this complaint, and she had been referred for an endocrine study. She also complained of a pain in the sacro-iliac region. She became dyspneic on the slightest exertion and was very fatigable. The family history was entirely irrelevant. The patient's own history showed a few minor ailments and a tonsillectomy and adenectomy some two years before. She had been married in the fall of the preceding year and had aborted an early foetus inside of three months. She described her headaches as sharp in character and aggravated by pressure. The face became flushed and there was a general feeling of malaise. The frequency varied from every other day to once a week, and their incidence was apparently not associated with any other event. She had several sore-throats since her tonsillectomy. She complained of intervals during which the nipples become red and sore and were painful. The menses began at the age of 14, were regular, and the periods apparently normal. Physical examination showed a well-developed, somewhat undernourished girl. There was a slight tenderness over the frontal sinus, poor occlusion of teeth and numerous small papules on the areolae of both breasts. The chest and abdomen were normal, and the remaining examination not informative. The urine volume was normal, elimination and balance poor; albumin was recorded, but the sediment was normal. The residual nitrogen was somewhat above the normal. The blood showed a slight but definite secondary anaemia with a slight lymphocytosis. The blood chemistry was normal; the serological tests were negative, the phthalein output somewhat low. The patient was 10 per cent under weight and the lung volume was somewhat below prediction. The basal rate was 29 per cent below the normal, and the pulse, blood pressure and temperature all definitely low. The sugar tolerance was 25 per cent below prediction. Alveolar carbon dioxide was a low normal value. Radiographs of the skull were normal. A pelvic examination disclosed a resistant mass in the region of the right adnexa, which was interpreted as either a cystic ovary or hydrosalpinx. The eye findings were normal.

Discussion: At the time this case was studied it was felt that the urine picture and the basal rate determined a thyroid failure, while the lowered sugar tolerance, coupled with the results of the pelvic examination, were interpreted as indicating some degree of ovarian failure. In the light of later experience it seems doubtful if this case warrants a pluriglandular diagnosis, as the dysfunctional state of

the thyroid (transition) would probably account for all of the departures from the normal. In view of the fact, however, that there was tangible disease apparently associated with one ovary, we have felt that in fairness this case should be retained as presenting a possible multiple glandular involvement.

CASE B-109. The patient's presenting complaint was given as indigestion, and the duration of the illness as 18 years, the condition following a bilateral oöphorectomy. The family history gave the death of the parents as from cardio-vascular disease; one of four sisters had hyperthyroidism; and one of five brothers died of hydrocephalus at eighteen months. The patient had been married for over 20 years, had borne one child and had one miscarriage and one ectopic pregnancy. She had had the usual illnesses of childhood, together with diphtheria, broncho-pneumonia 10 years previously, influenza at the time of the epidemic and cystitis several years before. She complained of occasional headaches, vertigo, and fainting spells. These latter she traced to peculiar sensations which would occur in her laparotomy scar. She reported occasional spasms of the epiglottis. She was greatly troubled with nausea and vomiting, which would occur usually an hour after eating. The bowels were constipated; there was some nocturia. The catamenia was established at the age of 16, was always irregular with increased interval and scanty flow until her operation terminated the function. Prior to her hysterectomy, a nephropexy had been performed and 8 years after she was operated upon for lysis of adhesions and had an appendectomy. Physical examination showed a well-developed and somewhat under nourished woman, nervous and garrulous, of about 50 years of age. The hair was thick and soft and that on the body was normally distributed. The teeth showed much dental attention; the thyroid was not enlarged; the lungs and heart substantially normal, and there was some tenderness in the right lower quadrant. The remaining examination was not significant. The urine volume was normal, elimination and balance poor; albumin was recorded, and the sediment showed much epithelial debris, numerous leucocytes and a few blood discs. The residual nitrogen fraction was positively high. The blood showed a marked lymphocytosis. The blood chemistry was normal except for a somewhat high blood sugar which was not verified on subsequent examinations. The serological tests were negative. The phthalein test was normal. The sugar tolerance was normal for one with the patient's gonad deficiency. Alveolar carbon dioxide was definitely low. The patient was 14 per cent under weight and with a somewhat depressed lung volume. The basal rate was —30 per cent, with low blood pressure, slow pulse, and somewhat low body temperature. The urea curve was normal. The eye examination showed slightly enlarged blind spots, but otherwise normal. X-ray plates showed a normal skull and sella, together with normal heart and lungs. A gastro-intestinal series of plates was normal. A pelvic examination gave results in accordance with the patient's history. A genitourinary examination defined an existing cystitis. A neurological examination failed to disclose evidence of organic nerve lesion. The patient had had, however, psychotic episodes in the past, was distinctly psycho-neurotic at the time of her examination, and some time after her discharge had an acute psychotic episode.

Discussion: Analysis of the data here demonstrates a thyroid failure superimposed upon the surgical hypogonadism. Naturally, with the patient's stormy surgical history, the bladder condition, and

the mental and nervous instability, the picture lacked the clarity of outline of an uncomplicated thyroid failure. Thyroid medication was advised and for a time was followed with marked evidence of clinical improvement. Later contact with the patient has been lacking.

CASE B-599. The patient was a woman of 54 complaining of headaches and of fatigability. The former condition had obtained for the preceding three years, occurred at intervals of approximately four weeks, and lasted from one to three days. The pain started in the left occipital region and usually extended forward to the left parietal or even the left frontal. It also radiated downward to the shoulder and arm. Simultaneously there was pain in both feet in the region of the arches. The rhythmic occurrence of the headache would suggest an association with the menstrual cycle which, however, was denied by the patient's history. The menses had been established at the age of 14, and six years later a pan-hysterectomy was performed. The inference drawn from the history was that this somewhat drastic method was adopted to correct extremely painful and debilitating periods. An interesting statement made by the patient in connection with the headaches was that they were always preceded by a period of "black rage," caused by some trivial event, and that they were always followed by periods of profound exhaustion. The family history was not significant. The history included the minor ailments of childhood, attacks of rheumatic fever at 16, at 20, and at 30, the last of these being followed by an arthritis of several years' duration, but without apparent cardiac complications. There had been several nervous breakdowns during the patient's life. She had had abscessed ears requiring operation. At the age of 7 she was struck on the head by a railroad gate and was rendered unconscious for several hours; again, at 14, trauma to the head caused another period of unconsciousness. Beside her hysterectomy she had had a gall bladder operation 8 years previously and, more recently, a tonsillectomy. She had been over weight for a number of years, a condition only partly controllable by dieting. She stated that she was nervously unstable, easily frightened and tended to be irritable. At the age of 12 she had a severe attack of psoriasis, which lasted for about a year and a half. She apparently had a food sensitivity to eggs. Physical examination showed a somewhat obese woman in the middle fifties. She was moderately deaf, but the remaining findings were practically normal. The urine volumes were normal, elimination was fair, the balance poor and the remaining examination negative. The nitrogen partition was normal. The blood showed a slight secondary anaemia and was definitely lymphoid. The blood chemistry was normal; the serological tests were negative; the phthalein output was normal. The sugar tolerance showed a negative response to 20 grams and a positive response to 30. This would indicate an increased tolerance for one in the patient's gonadal condition. She was 31 per cent overweight and had lost nearly half her predicted lung volume. The urea curve was normal. Alveolar carbon dioxide was at a normal level. Her basal rate was reported as —21 per cent, with low blood pressure, pulse rate, temperature and respiration rate. The patient was outwardly calm, but confessed to a definite nervousness, evidence of which she had concealed. A pelvic examination gave results in harmony with the patient's earlier history. An endermal test showed a negative response to egg albumin. A nose and throat examination showed a slight septal deviation. X-ray examination of the skull showed a slight elevation of both tables, posterior to the junction of the coronal and sagittal sutures; the sella was small

and regular; the frontal sinuses were irregular and blurred in outline, a condition consistent with an old sinusitis. The audiogram showed a loss of hearing in both ears, more pronounced in the higher frequencies. The eye examination showed normal fundi, enlarged blind spots, and a marked cutting of the upper form field demonstrably due to drooping lids. The neurological examiner commented on the evidences of an earlier frontal sinusitis and possible fracture of the skull in childhood, but failed to discover any evidence of organic disease.

Discussion: Taking the results produced by the patient's castration, it is obvious that a second possible endocrinopathy is superimposed on the surgical condition. With the increased sugar tolerance and moderate depression of the basal rate, one would instinctively think of a pituitary failure as the underlying functional endocrinopathy. The history of the blow to the head would also turn attention in this direction. Further analysis, however, makes the case for the pituitary much less certain. The physical findings associated with the basal rate determination are of the lower order of thyroid and not that of pituitary failure. Again, the blood shows only a lymphocytosis, there being no increase in the eosinophiles. The blood uric acid was normal. The basal rate was at least 21 per cent below prediction and there was every probability that the true rate fell somewhat below this. The sugar tolerance would seem to offer a stumbling block since there is a definite increase here wholly disproportionate to the magnitude of any probable thyroid failure. This patient was castrated within six years of the establishment of the menstrual function and thirty-four years before the time of study. As one of us has reported elsewhere, opportunity had occurred to study another patient who, like the present one, had been castrated at a very early age and many years before the study was carried out. She, too, showed a sugar tolerance of 30 grams. It seems possible, although the suggestion is offered only tentatively, that with early castration and the subsequent lapse of several decades, some sort of a compensatory process might have come into being. Another possible explanation could be that the thyroid failure was of such a magnitude as to condition an increased tolerance. While the lowering of the basal rate was of very moderate proportions, the value observed was certainly above the truth. Whether this assumption be correct or not, the present patient patently presents an endocrine disorder superimposed upon her surgical hypogonadism. The thyroid seemed to us more probably at fault, and the opinion was offered on that basis. The controlled use of thyroid medication was recommended.

CASE B-662. This patient came for study complaining of overweight, although she was 8 per cent below prediction. Subsequent knowledge of this fact by the patient did not influence her earlier conviction. She also reported herself as markedly fatigable and she complained of a swelling of the hands and wrists. She dated all of her complaints from the birth of her only child, an event that had taken place some 11 years before. She was delivered by Cæsarean section and at this time a pan-hysterectomy was performed. Within a few weeks of her operation she was obliged to take a long and fatiguing journey, and shortly after this her hair began to fall out. Under treatment this condition was corrected. Prior to her successful pregnancy the patient had frequently conceived, but had uniformly induced abortion, the total number of which she had forgotten. The family history included cardiac disease in both parents, tuberculosis

in a surviving brother and several other brothers who died in early infancy. In her own history, she reported minor ailments in childhood; a very severe case of influenza during the War, which she was told left her with an impaired heart, and a record of several nervous breakdowns. For a short time in the previous year she had suffered intermittently from precordial pain, but had had no attacks recently. She stated that she had a large appetite and, in the main, a perfectly functioning alimentary tract. Under the stress of nervous excitement, however, she had a tendency to vomit. She established the menses at the age of 11, and the function continued normal and regular until her castration. Physical examination showed a well-developed woman in the earlier forties. The hair was somewhat scanty, that on the body showing a normal distribution. Percussion demonstrated a possible cardiac enlargement; the blood pressure was definitely low. There was tenderness in both lower quadrants of the abdomen and some question of the tendon reflexes. The urine volume was normal, elimination fair, balance poor; albumin was recorded, but the sediments were normal. Her protein intake was below a maintenance level; the nitrogen partition formula was substantially normal. The blood showed a slight secondary anaemia, a distinct lympocytosis, and a slight eosinophilia. The nitrogenous constituents of the blood were all slightly above normal, the uric acid showing the smallest relative increase. The serological tests were negative. The phthalein output was below normal, the sugar tolerance normal. She was 8 per cent underweight, with a substantially normal sitting height index. The lung capacity was unimpaired. The urea curve showed fair elimination. The basal rate was —25 per cent, with marked depression of the blood pressure and temperature and a somewhat slow pulse. A heart examination gave no evidence of organic disease nor did the cardiogram, failing to confirm the earlier reports. In the examiner's opinion her cardiac symptoms were of functional nervous origin. The neurological findings were normal, failing to confirm the findings earlier reported. A pelvic examination yielded results in accordance with the patient's history. The eye examination showed some vascular sclerosis and otherwise normal findings.

Discussion: The patient was a markedly neurotic individual, presenting in a striking degree the insistent egocentricity of the gonad failure. She was wholly incooperative, a fact which influenced some of the tests and precluded the securing of others. She was wholly disingenuous in regard to her history; such statements as we have recorded above are, so far as we know, fairly accurate. There was no question that there was a surgical hypogonadism. Superimposed upon this was a second endocrine defect. With the level of her basal rate, with the normal sugar tolerance, the evidences of lowered kidney permeability, the normal eye findings, to name but a few, the thyroid seemed to be the most probable focus of failure. Thyroid medication was advised. This case falls technically into the group of pluriglandular syndromes. Its multiple character, however, derives from the surgical operation.

CASE B-976. This case presents unusual points of interest, as it gives the details of the study of a male castrate with a second superimposed endocrine defect. The patient was a man 67 years of age who gave as his chief complaint a sexual disorder. The history showed that 35 years previously (November, 1892) he had had a fall from a bicycle and struck his head and was rendered unconscious for several hours. He had a few days of convalescence and then re-

turned to work, apparently none the worse for the experience. Six months later he began to be troubled by indigestion associated with nervous exhaustion and occasional fainting spells. At about this time he found that sexual intercourse had become distasteful and was followed by a dull headache. In a very short time he lost all sense of desire. He was placed under treatment and began to improve. With his improvement sexual desire returned, but there was premature ejaculation, and this disturbed him greatly. He had been married some two years before his accident and his wife had borne one child, a daughter. The unsatisfactory character of his marital relationship gave rise to a marked emotional instability that seemed to amount to a psychoneurotic condition consisting mainly of a phobia of sexual intimacy. Two years after the accident he had a small hydrocele, and this was corrected with removal of the testicle. A year later he was advised to have the other testicle removed to correct the mental condition, and in the face of opposition by a consulting physician complete castration was performed. This second event was in 1898, or 30 years before his admission for this study. Between 1898 and 1901, rest and treatment by a neurologist gradually brought about some improvement. As a result, he was able to resume work and to reestablish his financial independence. This later condition obtained from 1901 to 1914; there was some continued improvement, and the occasional severity of the nervous instability did not prevent employment. Again, two years later, he developed urinary symptoms and cystoscopy demonstrated a stricture. Dilatation with sounds produced some betterment. A year later the veramontanum was removed. Following this operation he had a phlebitis in the left leg. In spite of his gonad defect, for a number of years close association with women had produced marked reactions which he called sexual disturbances. During this interval he had been aided somewhat by psychoanalysis and in 1923 a course of steam baths brought temporary relief. A course of treatment with orchic material was followed by a recurrence of the earlier symptoms and led to a discontinuance of the therapy. Subsequent to this he was given a brief course of thyroid therapy which, as it was based on basal rates which were always reported as within the normal range, never exceeded a dosage of more than one grain a day. This treatment yielded no result, and two years prior to admission to this Clinic the patient had come under the control of a clinical psychologist who had produced very marked improvement in the neurological and mental picture. As there were obviously physical difficulties as well, our study was undertaken to ascertain the patient's functional level. It should be mentioned in passing that the reason given for the second orchidectomy was to eliminate pain in the pudic nerve. The family history showed a rather remarkable longevity in his immediate relatives and one case of epilepsy in a brother. As noted above, he had been married and his wife had borne one child prior to his mutilation. He reported relatively few ailments outside of those recorded above. "Inflammation of the bowels" at 16, mild diphtheria at 20. and several traumatic injuries to the extremities were reported. He complained of head pains starting in the occiput and radiating forward, but not of true headaches. There had been some loss of hearing in the left ear. His teeth had always been poor, and while under his endocrine medication he had periods of "nerve aching" in the jaws. During his long illness there had been brief periods when he was slightly jaundiced, and he complained of more or less gastro-intestinal disturbance for the preceding four decades. He recorded tenderness along the course of the sciatic nerve, also tenderness on both sides of the lumbo-sacral spine.

Throughout his illness he stated that he had been very nervous and irritable and was introspective, readily excited and emotional. The psychologist found a history of anxiety neurosis, but there was no hallucinations or delusions. He had been markedly fatigable for many years. Physical examination showed a well-developed and nourished man with a tendency toward obesity in the abdomen and chest wall. The protuberant abdomen determined a poor posture, increasing the lumbar lordosis. The hair on the vertex was steel gray and moderate in amount. The pupils showed a sluggish light reaction and a beginning arcus senilis was noted. There was apparently a bilateral deafness. The teeth were in fair condition, the tonsils apparently not offending. The heart, lungs, and abdomen were normal. The penis was short and small, the scrotum small and empty. The sparse pubic hair was of female distribution. In addition to the lordosis noted above, there was a moderate right lumbar scoliosis, a tenderness on palpation at the levels of the seventh thoracic and about the lumbosacral joint; also some tenderness on pressure in the right portion and along the courses of the sciatic nerves. The cranial nerves were intact. The normal reflexes were active. The train and content of thought were normal, and the routine neurological findings otherwise normal. The urine volume was normal, elimination fair, balance good. Albumin was recorded in both specimens. The nitrogen partition showed a somewhat high residual fraction. The blood showed a slight but definite secondary anaemia. There was a relative increase in the endothelial leucocytes and a slight relative increase in the eosinophiles. The nitrogenous constituents of the blood were all slightly above the normal. The serological tests were negative. The phthalein was definitely low. Galactose tolerance was somewhat depressed. He was recorded as 14 per cent overweight, but was actually in excess of this, as the sitting height index was high. There was a perceptable loss of lung volume. Alveolar CO_2 was at a normal level. An urea index was a low normal value. The basal rate was 30 per cent below predicition, with bradycardia, sub-normal temperature, and low blood pressure. A genitourinary report indicated normal conditions. Repeated examination of the patient's stools showed no parasites, ova or blood. An ear examination gave normal findings. The audiogram showed loss of hearing, which was more pronounced in the upper register. The Barany test findings were normal. The blood fragility was normal. A neurological examination gave no evidence of organic disease. A cardiogram was substantially normal. The eye examination showed normal pupillary reaction, yellowish discs, some vascular sclerosis, and a cutting of the upper form field, due to drooping lids. An orthopedic examination confirmed the existence of a low backstrain. Radiography showed a proliferating arthritis of the right astragulo-scaphoid articulation; the right sacro-iliac joint picture was hazy and indistinct, and there were asymmetrical articulations in the 4th and 5th lumbar region. There were hypertrophic spurs on the dorsum of the right foot. The skull, sinuses, and sella were normal. The teeth were not diseased. A gastro-intestinal examination gave normal findings. A Graham test by the intravenous route was also normal. The patient had a slight skin eruption on the lower left leg which was defined in a dermatological examination as a mild erythematous eczema. The icteric index and Van den Bergh tests gave normal findings, but an examination of the duodenal contents by the McClure technique showed a marked liver dysfunction. A very full statement of the mental aspects was made available through the courtesy of the referring psychologist. It does not lend itself, however, to presentation in abstract form.

Discussion: Experience with other male castrates has demonstrated that the condition produces but minor changes in the level of vital function tests. With due recognition of this fact, the picture presented by this examination shows a clear-cut thyroid failure of considerable magnitude and probably of long duration. The demonstrated liver dysfunction explains the somewhat lowered sugar tolerance. Apparently this difficulty was confined to the liver and did not include the gall bladder. An interesting feature in this case is the failure of the lowered thyroid activity to produce a lowered sexual level. That his sexual abnormality, however, was confined to the mental reactions and secondary sexual emotions and was probably engendered in part, at least, by psychogenic factors, explains in some measure the presenting anomaly. In our experience, male castrates are relatively rare, at least those who are willing to undergo investigation. We feel particularly fortunate in the opportunity to have studied this case, which conventionally falls in the pluriglandular group.

CASE S-1843. The patient's chief complaint was of ready fatigability, coupled with pain over the sternum and radiating to the left shoulder. She was also extremely nervous. The patient was 48 years of age at the time of the study and had matured at the age of 17. The periods were very irregular, with both increase and diminution in the interval. The flow was profuse. Three years and a half before admission she flowed steadily for a period of six months. Operation was recommended and the ovaries and uterus removed. Up to that time the patient's health had been good. Her present difficulties, she felt, dated from the operation. Within the preceding six months the pain and a numbness of the fingers of the left hand had developed. The family history included that of the mother's death of cancer, the father's from gangrene. The patient had been married 30 years, had always desired children, but had never conceived. She reported only minor ailments, pneumonia at the age of 5, and a nasal operation many years before. Fifteen years previously she had been struck by an automobile, and although she sustained no fractures, was placed in a jacket for a few months; she had shown no symptoms subsequently. Some six years before she began to have severe headaches, but these disappeared after her operation. For a number of years there had been a gradual loss of hair and slow, progressive impairment of vision. For the past few years she had had occasional attacks of dyspnoea. She had a tendency to constipation and stated that she found it necessary to remove the feces manually. Her physical examination showed fair development and nourishment, some thinning of the hair on the vertex, and body hair normally distributed. The eyes were normal. The tonsils were open to suspicion. There was no thyroid enlargement. Heart, lungs and abdomen were normal. The skin was dry and atrophic and there was some hypertrichosis on the upper lip and chin. The routine neurological findings were normal. The urine was scanty, the elimination and balance poor. The nitrogen output indicated an inadequate protein intake; the partition formula was substantially normal. The blood showed a lymphocytosis and a slightly high value for the nitrogenous constituents; the serological tests gave normal findings. The 'phthalein output was below normal; alveolar CO_2 at a normal level. She was recorded as 4 per cent below her predicted weight, with a significant loss in predicted lung volume. The basal rate was —24 per cent. The sugar tolerance was normal for her castrate condition. The pulse and temperature were distinctly low. The blood pressure showed an upward tendency,

although falling far short of a hypertensive level. A nose and throat examination showed a minor septum deviation and unoffending tonsils clearing the earlier finding. A cardiogram confirmed the bradycardia and was otherwise negative. The eye examination showed poor convergence accommodation, marked cutting of the upper form fields from lid droop, and slightly enlarged blind spots.

Discussion: In addition to the surgical hypogonadism, the patient had a fairly typical thyroid failure, without myxedema, which was probably of long standing. Technically, the case is pluriglandular. It would be interesting to speculate on what would have been the influence of thyroid medication on the excessive menstrual flow which led to the patient's castration.

Group III-b. Thyroid Dysfunction and Gonad Failure

Case S-179. The patient's chief complaint was of weakness and dyspnoea. The condition followed operations in two stages for the partial removal of a hyperactive thyroid. After the second operation the patient had gradually become fatigable and developed a lack of strength. She had been much underweight as a result of the earlier toxic thyroid and had gained 40 pounds in the interval. During the past two years she had been greatly troubled with hot flashes and had noted coincidentally a marked diminution in the menstrual function. Previous menstrual history showed maturity at 12 and a regular rhythm with somewhat excessive flow. She had been married 17 years and had borne two children without miscarriage. Her family history was not relevant. The patient had had minor ailments, together with scarlet fever at 16, typhoid at 18, the two thyroid operations already noted, a ventral suspension of the uterus, and two repair operations on the vagina. She stated that her teeth were very sensitive and required constant care. The year before she had had a brief attack of indigestion. The bowels were regular. Recently she had developed a slight vulval pruritus. Physical examination showed good development and nourishment. The patient was somewhat slow in her physical and mental response. The skin was moist, the hair normal in amount and distribution. There was no residual thyroid enlargement. The heart, lungs, and abdomen were normal, as were the structures considered in a routine neurological examination. The urine volume was normal, elimination and balance poor; the findings were otherwise normal. The nitrogen partition examination showed an inadequate protein intake and a normal formula. The blood showed a slight leucocytosis, with increase in the neutrophilic elements. The blood was normal chemically. The serological tests were negative. The 'phthalein output was somewhat below normal; alveolar carbon dioxide was definitely low. The patient's observed weight corresponded with prediction. There was some lessening of the lung capacity. The basal rate was reported as —11 per cent, with a slightly rapid pulse, a slightly febrile temperature, and a very low blood pressure. Radiography of the skull, sella and chest showed all these structures to be normal.

Discussion: It is a question in our minds whether this case properly belongs in the pluriglandular group. There is patently a thyroid dysfunction dating from the earlier overactivity. The history of the recent pruritus suggests a possible glycosuria, although the specimen of urine examined was sugar free. The blood pressure was very low. The alveolar carbon dioxide was below the normal. Additional opportunity for observation was requested on this patient, but could not be

secured. While we do not regard the case as clearly belonging to the pluriglandular group, we feel that there are enough evidences to warrant the suggestion of a gonad failure superimposed upon the thyroid condition.

CASE S-230. This patient offered an interesting study, as both of her two endocrinopathies existing at the time of study had surgical backgrounds. Sixteen years before admission the patient noted a glandular enlargement in the neck. Medical consultation defined a cardiac insufficiency, and the patient was hospitalized for rest. During her stay in the hospital she was given tuberculin for the glandular condition. This treatment produced no result, and subsequent x-ray treatment was ineffective. Three years before her admission to this Clinic the neck condition was diagnosed as a goiter and a portion of the gland removed. At about the same time she was also operated upon for a uterine fibroid and a bilateral ovariectomy was also performed. Prior to the removal of the thyroid the patient experienced no symptoms which she felt could be referred to the condition. The family history was negative. The patient had had the usual childhood diseases, and rheumatic fever 35 years before. The menstrual history was entirely normal up to the time of her laparotomy. Her remaining history was entirely negative. The physical examination showed a well-developed and somewhat obese woman of 48. Beyond the scars of her two operations the only point of significance lay in a systolic murmur at the apex of the heart which was transmitted to the axilla. There was apparently an aortic insufficiency and regurgitation. The urine volume was scanty; elimination and balance were poor. The urine contained less than a gram of sugar and was otherwise normal. The blood was markedly lymphoid, and there was a slight secondary anaemia. The blood was normal, chemically. The serological tests were negative. The 'phthalein output was normal. Her alveolar CO_2 was of normal value. The patient was 20 per cent overweight and about 30 per cent below her predicted lung volume. A fairly satisfactory basal rate was 6 per cent below prediction, with a somewhat low blood pressure, normal pulse and temperature.

Discussion: There can be no question in this case as to a lowered gonad activity, but the level of the thyroid function cannot be so simply resolved. It would seem probable that the lowering of the basal rate produced by castration was compensated by a residual slight hyperactivity of the thyroid. The lowered sugar tolerance was referable to the gonad condition. Its principal interest, in our opinion, lies in the slight departures from the normal produced by two multilating operations which produced a condition in which there was a very definite degree of mutual compensation.

CASE S-988. The patient's chief complaint was of intense nervousness and fear, coupled with difficulty in breathing, excessive perspiration, and palpitation. She had a very marked thyroid enlargement and was somewhat obese. The mother had a goiter which began at the age of 25, and when the patient was 23 (26 years ago) she noted that her own thyroid was beginning to enlarge. It grew slowly for a number of years, then remained stationary for a still longer interval, but had begun to grow again in the preceding three years. With this second growth period the majority of her symptoms had developed. The choking sensation in her throat was one of her principal difficulties. She had been obese for a number of years. Some 10 years before both ovaries had been removed and her obesity

apparently began after this operation. The family history, outside that of the mother, showed only diabetes in an uncle. The patient had been married for 20 years and had borne two children without miscarriage. The additional records showed only minor ailments, recurrent sore-throats, an occasional dull headache, and some loss of vision. She believed that the eyeballs had protruded slightly during the last few years. A tonsil and adenoid operation a number of years ago had diminished but not eliminated her tendency to sore-throat. The gastro-intestinal history was not suggestive. The menses were established at 15 and were always irregular with an erratic rhythm. Physical examination showed a moderate obesity. There was some difficulty in breathing, a slight suggestion of exophthalmos, hypertrichosis on the lip and chin, excessive pilosity on the limbs, but female distribution of pubic hair. There was marked thyroid enlargement and forward or backward movement of the head produced difficulty in breathing. The heart and lungs were normal. There was an ill-defined tenderness in the abdomen on deep pressure. The extended fingers showed a fine tremor. The urine volume was slightly low; elimination and balance were poor. Albumin was recorded; the findings were otherwise normal. The protein intake was ample; the residual nitrogen fraction much above the normal. The blood showed a slight secondary anaemia and a 66 per cent lymphocytosis. The blood analysis showed slight increase in all of the nitrogenous constituents. The serological findings were normal. The phthalein output was low, and the alveolar carbon dioxide, normal. The patient was 36 per cent above her predicted weight and 40 per cent below her predicted lung volume. The basal rate was —13 per cent, with a somewhat rapid pulse and lowered blood pressure. Radiography showed a normal sella and normal mediastinal shadow. An examination of the mouth showed many dubious teeth, heavily crowned. A nose and throat examination showed hypertrophied, infected tonsils and a non-obstructing septum deviation. A neurological examination disclosed no abnormalities. The eye findings were practically normal. Her sugar tolerance was depressed slightly below the level conditioned by her castration. A repetition of the basal rate a few weeks later gave a level of —1 per cent, with a somewhat more rapid pulse.

Discussion: The patient's surgical hypogonadism determines one factor in her pluriglandular definition. She also had a definite thyroid enlargement which we were inclined to believe was in a dysfunctional state. If the thyroid were slightly overactive it would exercise a compensating influence in the lowering effect of the castration. It would also account for her lowered sugar tolerance, as has been noted at length in an earlier thyroid paper. While again the case is not clear cut, the bulk of evidence pointed to a thyroid dysfunction superimposed upon a surgical hypogonadism. Both were of long standing. The patient was not regarded as a suitable subject for operation at the time, but was advised to remain under observation in anticipation of a change in the level of thyroid activity. Iodine medication was suggested. A year later the patient returned for a repeated study and showed almost identically the same picture as that first presented. The significant changes were a loss of some 13 kilograms in weight, an increase in the evidences of kidney impairment, and a definite increase in the thyroid size. In spite of these disadvantages, the patient reported herself as feeling very much better, except for increased difficulty in breathing. There was no change in the relative basal rate. Operation was recommended with a view to correcting mechanical interference with breathing, and a large tumor mass was

removed which was reported by the pathological laboratory staff to be a colloid goiter. The patient is to return for further study in the near future.

CASE S-1023. The patient's chief complaint was of deafness, coupled with flatulency, vomiting and gastric discomfort without pain. This condition had developed some 10 years before admission, at the time of her marriage at the age of 29. The condition was progressive for some 5 years, and 3 years ago an operation was performed for lysis of adhesions. No immediate improvement was manifested, but after a few months she improved definitely and the vomiting became very infrequent. Eighteen months before, however, she began to vomit once or twice a week, gradually increasing in frequency to three or four times a week. On one occasion the vomitus contained fresh blood. More recently, intermittent pain in the right hypochondrium had developed and also in the right lower quadrant. The bowels showed alternating periods of constipation and diarrhoea. The family history was entirely normal. The patient had been married for 10 years without pregnancy. Subsequent questioning developed the fact that she had had both ovaries removed 24 years before, at the age of 15. We could not ascertain the reason for this operation. She offered the usual history of minor ailments, an appendectomy at the time of her ovariectomy, and influenza during the epidemic. She complained of an occasional headache. Her deafness was of about 13 years duration, had been progressive and accompanied by tinnitus, vertigo, and paracusis. The history, while not clear cut, offered some evidence of an earlier otitis. She was subject to head colds, had a nasal obstruction, had had a pyelitis in the previous eighteen months; this had yielded to treatment. The catamenia had been established at 11, and was regular and scanty up to the time of her artificial menopause. Physical examination showed fair development and nourishment. The hair on the vertex was thin and coarse; there was no marked hypertrichosis. The aural acuity was distinctly impaired. The thyroid was not enlarged. The heart, lungs, and abdomen were substantially normal. There was a minor cervical adenopathy, some tenderness in the mid-dorsal region of the spine, and normal routine neurological findings. The urine volume was normal; elimination and balance, poor. Albumin was reported. The nitrogen partition was normal. The haemoglobin was low, the blood cells normal in relative numbers. The blood showed high uric acid, which was not confirmed by later examinations. The 'phthalein, CO_2, and vital capacity measurements were substantially normal. The serological findings were normal. An unsatisfactory basal examination showed —14 per cent, with rapid pulse, a slightly febrile temperature and a downward tendency to the blood pressure. Eye examination showed enlarged blind spots and a slight contraction of the color fields. The audiogram showed marked loss of hearing in both ears. The patient's sugar tolerance coincided with the level produced by castration. A radiographic series of gastro-intestinal plates was normal.

Discussion: This case presented several points of obscurity. When the patient was first seen the lowered sugar tolerance, the high blood uric acid (subsequently found to be in error), and certain points in the history suggested a possible pituitary condition. Additional observations were requested in the course of these, and as the result of questioning, the patient told of her castration at the age of 15. As stated above, we could not learn the cause of this operation, but the fact that it had taken place naturally influenced the interpretation

of the findings. Some additional measurements were secured, although not all that were requested. The patient had a definitely low basal rate, although we could not ascertain its real magnitude. It was felt that there was some evidence for the existence of a possible thyroid dysfunction complicating the surgical hypogonadism. The patient was not entirely cooperative, and it has been impossible to verify the tentative conclusion. The case is offered as one of a somewhat doubtful pluriglandularity in which gonad failure is established and the thyroid disturbance a matter of possibility.

CASE S-1069. The patient's chief complaints were of a general fatigability, palpitation, and arthritis. Four years before admission she developed an acute attack of arthritis, localized in the left hand and complicated with a cystitis. Under treatment both conditions cleared up in about six weeks. Following these, her fatigability developed. There had been an earlier history of arthritis, somewhat obscure in definition, and generalized as to distribution. The patient had been troubled with sore-throats, but these had yielded largely to a tonsillectomy 2 years before. For several years the teeth had also been a cause of difficulty and a year previously three had been removed, all of which showed abscessed roots. She had had palpitation for the past three years and occasional attacks of precordial pain during the last year. The family history was not especially significant. The patient had been married for 20 years and had borne two children without miscarriage. In addition to the minor childhood complains, she had had small-pox when three months of age. Her surgical history included a repair operation, the removal of one cystic ovary, and, later, a complete castration, an appendectomy, and two tonsillectomies. She had been subject to headaches, but these had been helped somewhat by glasses. There was some loss of hearing in the left ear, and some obstruction of breathing on the left side. She experienced considerable vascular disturbance after the removal of her second ovary. She was constipated and had worn a brace for 15 years for gastroptosis. The menstrual history was not remarkable. She complained of trouble with the sacro-iliac joint for the past 16 years. Her physical examination showed good development and nourishment and substantially normal conditions throughout. The urine volume was normal, elimination and balance poor; albumin was recorded. There was a high residual nitrogen fraction. The blood showed a low haemoglobin and marked lymphocytosis Her non-protein and urea nitrogen were high and uric acid was normal. The serological findings were normal. The phthalein output was normal; alveolar carbon dioxide presented a normal level. The patient's observed and predicted weight agreed; there was some loss of lung volume. Earlier basal rates had shown definitely depressed values. The patient had been under intermittent thyroid medication and at the time of this test a not satisfactory observation was 12 per cent below prediction. The patient was both restless and nervous and the true basal rate was undoubtedly much lower. The blood pressure was low, the pulse normal, but the earlier records had shown a definite bradycardia. Her cardiogram was normal, as was a radiogram of the teeth; the audiogram showed some loss of hearing in both ears, most marked in the lower register; the eye findings were normal. The patient's sugar tolerance was midway between the normal and castrated level.

Discussion: The findings in this case were not entirely clear cut, as there was not full cooperation and the history of the earlier thy-

roid medication not entirely complete. That the patient had a surgical hypogonadism was established. Superimposed upon this there seemed to be an unquestioned thyroid failure of some degree of severity. As a thyroid failure may raise the sugar tolerance slightly, it was felt that the patient's value reflected the composite influence of both thyroid dysfunction and of the missing ovaries. We have learned indirectly that consistent thyroid medication has produced some betterment.

GROUP IV. THYROID DYSFUNCTION WITH HYPOGONADISM AND POSSIBLE PITUITARY DYSFUNCTION

CASE B-164. That this case is one of a pluriglandular involvement admits of no doubt. The degree and extent of such involvement, however, is in part uncertain. We hold no brief for the accuracy of the complete diagnosis. The patient when first seen was a woman of 40, complaining of nervousness, dyspnoea, choking sensations in the throat, headache, palpitation, loss of hair and occasional swelling in the left leg. Her difficulties apparently began some four years previously, when she became dyspnoeic following what she described as a "heat stroke." It was noted that she had been markedly fatigable prior to this. During her convalescence from the "heat stroke" she was hospitalized and a systolic blood pressure of 240 recorded. On her discharge she visited another hospital, where a diagnosis of thyrotoxicosis was made. A series of metabolism tests gave basal rates varying from +23 per cent to +8 per cent, the majority of them being well within the normal range. Operation followed the diagnosis and the left portion of the thyroid was removed. Prior to the operation the left leg had become sensitive to touch, and there was a burning sensation in it. All of her symptoms improved greatly after the operation, but in a few months they all returned with increased severity. A physician whom she consulted suggested further manipulation of the thyroid function by x-rays, but her previous surgeon advised strongly against any further thyroid interference. Her symptoms increased in severity and she consulted a new practitioner, who informed her that she had a cystic ovary, which he removed, at the same time ligating the thyroid artery. During this period (2 years) the patient was having very profuse menstrual periods at two months' intervals. Following her ovariectomy and thyroid ligation, she had regular periods for four months and then irregularity set in, with increased interval and very profuse flow. During her periods the thyroid region became swollen and a transitory skin eruption developed. She had diarrhoea also at these times. Her last operation left her in a worse condition than previously, and she was ultimately referred to this Clinic for study. With one ovary removed, a portion of the thyroid ablated and the thyroid artery ligated, she presented an interesting endocrine study. The family history was wholly irrelevant. The patient had the common childhood ailments and chronic intestinal disturbance from 17 to 30, which terminated in an intestinal obstruction, for which she was operated upon, with the removal of the appendix. She did not know if anything else were done at this time. The intestinal symptoms cleared up within a year of this operation. She had had a tonsillectomy and adenectomy 9 years before. During the thirteen years of her intestinal trouble she suffered from severe headaches. There was temporary relief after the operation, but they had returned with increasing intensity during the past few years. For many years the patient had been subject to severe epistaxis, her teeth had always been poor and soft, she had a palpitation all her life, and was highly

susceptible to respiratory infections. She had a tendency to constipation. The menses started at 14, the history of the interval having been given above. She had hay-fever every August. She had become considerably overweight, the excess being confined to the abdomen and hips. Physical examination showed a restless, poorly developed woman less than 4 ft. 11 in. tall and with a pronounced localized girdle obesity. The hair on the vertex was thin, the mouth showed an anatomical peculiarity with bilateral ridges under the tongue. There was a tenderness on deep palpation in the left lower quadrant. The left leg showed an enlarged calf with a hardened area, which the patient stated was associated with a venous thrombosis. She also stated that there had been a similar condition in the right leg. The remaining findings were normal. The urine volume was slightly high, elimination and balance good. All specimens showed albumin and, one, fine granular casts. The nitrogen partition was normal. The blood showed a slight lymphocytosis. There was no eosinophilia. Non-protein and urea nitrogen of the blood were above the normal level and the blood uric acid was 6 mgm., a value markedly above the normal. The serological tests gave no evidence of lues. The phthalein output was at the low borderline of the normal. The sugar tolerance was greatly depressed, the patient reacting positively with 10 grams, although no glycosuria had been recorded. The sitting height index was above 0.55. The patient was recorded as 22 per cent above prediction and actually was still more overweight. The lung capacity was 30 per cent below prediction. A urea curve showed a normal elimination. Alveolar carbon dioxide was below the normal. The patient's basal rate was within one or two per cent of prediction, but the recorded value was certainly somewhat high, as the patient was nervous. There were several tests, however, made independently, which were highly concordant. The pulse rate was somewhat rapid, the blood pressure showed the hypertensive level 190/110. The pelvic examination failed to demonstrate the adnexa. Radiographic findings of the skull, sella and sinuses were normal. There was no evidence of sub-sternal thyroid, and the heart and lungs were normal. The eye examination showed yellowish discs, enlarged blind spots, and a cutting of the form fields, more pronounced in the left eye and on the temporal side.

Discussion: This patient was seen a number of years ago, at a time when many of the more informative special examinations were not available. To summarize the endocrine status, she was a victim of partial, if not complete, gonad failure. Secondly, there was an earlier history of thyrotoxicosis which lacked support in the recorded basal tests, for which she had had both a partial removal of the gland and a ligation. That this might induce some degree of thyroid dysfunction would seem reasonable. A gonad operation would lower the basal rate somewhat. A compensatory residual hyperactivity of her thyroid remnant would raise it, but as it had brought it only to a normal level this thyroid influence could not have been a very marked one. The gonad failure could drop the sugar tolerance to 20 grams. A thyroid overactivity, to produce a further lowering, would probably be of considerable proportions, much more, at least, than those suggested by the basal rate. The patient was under 5 feet tall, she had a marked girdle obesity, an ample urine elimination, a very high blood uric acid, the significance of which is somewhat lessened by the slight increase recorded in the other nitrogen constituents of the blood; a lymphoid type of blood, a normal nitrogen partition, and low alveolar carbon dioxide, referable, presumably, to her gonad condition. On the basis of all these facts one could conceive of a pituitary disease which

had dated back to childhood. That she had a normal sella has no bearing on the matter, since many severe pituitary cases exhibit this condition. We are frankly in doubt as to the complete endocrine status of this case. Surgery has established the thyroid and in part the gonad condition; an initial and participating pituitary condition remains a matter of surmise. Our experience has led us to be very loath to place undue weight upon external appearances, but such observations as those of the eye examination and certain of the laboratory tests can be related to her known endocrinopathies with the greatest difficulty, if at all. With one ovary gone and the other possibly diseased, with a thyroid presumptively in a dysfunctional state, there still remain a group of objective findings that suggest even though they fail to define pituitary involvement.

BIBLIOGRAPHY

1. Rowe: This Journal, **12**: 1. 1928.
2. Rowe and Lawrence: Ibid. **12**: 245. 1928.
3. Lawrence and Rowe: Ibid. **12**: 377. 1928.
4. Rowe and Lawrence: Ibid. **12**: 591. 1928.
5. Keith: Lancet, **ii**: 553. 1919.
6. Berman: The glands that regulate personality. N. Y., 1922. MacMillan.
7. Falta: Endocrine diseases, Meyer's trans., 3rd ed. Phila., 1923. Blakiston.
8. Timme: This Journal, **2**: 208. 1918.
9. Drury, N. E.: J. Med. **199**: 168. 1928.
10. Reynolds and Macomber: Fertility and sterility in human marriages. Phila., 1924. Saunders.

THE VAGINAL SMEAR METHOD OF ASSAY OF THE OVARIAN HORMONE

LYDIA C. KAHNT AND EDWARD A. DOISY

From the Laboratory of Biological Chemistry, St. Louis University School of Medicine

ST. LOUIS

In a recent paper, Coward and Burn (1927) have expressed some doubt about the accuracy of the vaginal smear method (Allen and Doisy, 1923) of assay of the ovarian hormone. Their conclusion that the rat unit may vary as much as 1,000 per cent is so surprising that we have spent some time in developing more exactly some of the conditions which must be fulfilled to secure accurate assays. Prior to the appearance of the paper by Coward and Burn (1927) we had compared our assays with Laqueur and with a pharmaceutical house. In the first case we found 2.2, whereas Laqueur found 2.0 R. U. per 1 cc. In the second case, the commercial preparation was labeled 4 R. U. per 1 cc., but our result was 5 R. U. The remarkably good agreement with these samples and our other experiences with the routine assays of our preparations, had led us to believe that the vaginal smear method of assay is as reliable as other good procedures of assaying biological products. The data submitted in this paper seem to indicate that our faith was well founded.

Since it is important for the various laboratories (both chemical and pharmaceutical) interested in research on the ovarian hormone to be able to duplicate assays performed in other laboratories, we are giving in some detail the procedures that we have used.

METHODS

Animals: All rats used were albinos reared from our own stock, which has not been augmented from outside sources for over two years. Our animals are fed an adequate diet containing yellow corn, carrots, lettuce, milk, raw beef, dog cakes and cod liver oil. Since Evans and Bishop (1922, also Evans 1928) have pointed out that on a diet deficient in Vitamin A the tendency on the part of the vaginal mucosa to form cornified epithe-

lial cells is no longer limited to the time of growth, maturation and rupture of the Graafian follicles, but is continuous even in ovariectomized females, an ample supply of cod liver oil was provided.

Vaginal smears of female rats weighing from 90-110 grams at an age of 7-8 weeks were made daily for a period of at least two weeks, to determine the regularity of the oestrous cycle. Only those animals having regular cycles were used. The ovariectomy was performed under deep ether anæsthesia, aseptic precautions being observed. In removing the ovary care was taken to remove the tube and the surrounding fat, in order that no remnant of ovarian tissue might be left to cause trouble in the later work. The animals recovered from the anæsthesia promptly, the incisions healed rapidly and very few infections resulted from the operations. Daily vaginal smears were made for two weeks following ovariectomy, to determine whether all ovarian tissue had been removed. Negative smears were obtained in every case, indicating that the ovariectomy had been complete.

Injections: In our earlier work we attempted to simulate the ovarian activity by injecting preparations of the hormone in three portions given at four-hour intervals. This repetition of injection, of course, entails more work than a single injection, but our early experiments seemed to indicate that more uniform results were obtainable in this way. Laqueur (1927), Zondek (1926), and possibly others, have gone to the other extreme and administered six injections distributed over two or more days. While it seems to be true that a smaller quantity so supplied will produce the typical cornified cells, this procedure seems to possess little advantage over the injection in three portions, and, of course, has the disadvantage of requiring more work. As will be brought out in the discussion of our experimental work, animals receiving three injections respond uniformly enough to give satisfactory routine assays. It is important for workers to adopt a uniform number of injections, as the actual weight of the rat unit diminishes as the number of injections increases.

Some of our experiments seem to indicate that the extent of genital atrophy influences the amount of hormone required to produce a positive smear. We have, therefore, practiced what we term *priming.* Our test animals are used once a week, thus corresponding roughly to the length of the normal ovarian cycle

(4-5 days). In the event that an insufficient quantity of hormone is administered and a negative result obtained, the rat is *primed* the following week by the injection of a known extract containing 1.5 R. U. The following week the rat is again ready for use. It occasionally happens in our preliminary rough assays that the priming is omitted until a rat has two successive negative reactions, but in final accurate assays one negative reaction is cause for a priming injection.

Injections are always made subcutaneously. In agreement with Evans and Burr (1926), we have found that the results of intraperitoneal injections are less uniform.

Preparations Used: The preparations used, which had been previously standardized, were an aqueous solution, No. 15578, and two oil solutions, No. 30540 and No. 34072. We are indebted to the Digestive Ferments Company for the former and to E. R. Squibb & Son for the latter two.

Explanation of Symbols: Each smear spread over an area of 1 sq. cm. is stained and examined thoroughly with low power. The results of the vaginal smears are expressed by means of the following symbols:

+ nothing but cornified cells.

±±± predominance of cornified cells, but a few nucleated epithelial cells; no leucocytes.

±± cornified cells, nucleated epithelial cells and a *very few* leucocytes. The cornified and nucleated epithelial cells predominate; in fact, the number of leucocytes is so small that they may be overlooked unless a thorough examination of the entire smear is made.

± leucocytes, nucleated epithelial cells and some cornified cells.

— mainly leucocytes.

Though there has been considerable discussion (Laqueur, 1926; Loewe, 1926; Zondek and Ascheim, 1926) upon the estimation of activity from the smears, we have adopted the view that a predominance of cornified cells, with some nucleated epithelial cells and a *very few* leucocytes, should be taken as a positive reaction. Frequently a test animal is encountered which responds in this way to, for example, 0.25 cc., and on subsequent injection

of 0.40 cc. of the same preparation gives the same type of smear. We believe that the results of assaying will be more uniform by evaluating this reaction as positive, even though this smear is not the typical full oestrous smear of the normal female.

The smear ratings, +, ±±±, and ±± are taken to mean that the response is positive and that at least 1 R. U. has been injected. The ± means that a partial response to an insufficient dosage has occurred, but in our judgment it should be classed as only little better than the —. In the discussion, the +, ±±±, and ±± of our tables are grouped under the positive or + designation, while the ± and — are classed together as negative, or —.

RESULTS

Ovariectomized rats from No. 345 to No. 397, inclusive, were used in this study of the limitations of the vaginal smear method of assay. Twenty-five animals were injected with 0.27 cc. and 0.15 cc. of preparation No. 15578. From the results of a few preliminary tests it was found that 0.21 cc. contained 1 R. U. The two dosages given then contained 30 per cent more and 30 per cent less than 1 R. U.

Of the 25 animals injected with 0.15 cc., two gave a positive reaction; in fact, one of them (No. 359) gave a + response on three different trials. However, both of these animals failed to respond positively to 0.10 cc.

With the larger volume (0.27 cc.) all animals except No. 358 gave a + reaction. This rat furthermore gave a — reaction to 0.34 cc., but on another trial gave a + reaction. In two out of three trials No. 369 gave a negative response to 0.27 cc., but responded favorably to 0.34 cc.

Of this series of animals, a total of four, or 16 per cent, responded irregularly. The two worst offenders, No. 359 and No. 369, were discarded and not used for subsequent tests.

Eleven rats were used in the next series of experiments in which an oil solution was injected. Ten of the eleven animals gave a negative smear upon the injection of 0.18 cc. The response to a slightly larger quantity, 0.24 cc., in eight animals was +. Owing to an insufficient quantity of this preparation, the other three were injected with an approximately equal

quantity of another extract. Two of the three gave a positive reaction. Of this series, then, 2 of the 11 rats differed appreciably in their response. This is not surprising, since the smaller dosage was only 25 per cent less than the larger.

The third series is more extensive in that a greater range of dosage was employed. Of the 24 rats studied, 7 had been used in the second series. The irregularity previously exhibited by No. 378 and No. 380 is not apparent in the third series.

With the smaller volume, 0.15 cc. or 0.17 cc., 3 of the 24 animals gave a + reaction. Each of these gave a negative response upon repetition of this volume. When the dosage was increased to 0.25 cc., 12 of 23 animals gave a — reaction. In 8 animals of the 23 this volume was injected again, and in each case the former response was obtained.

Obviously, from the equal distribution of — and + reactions, 0.25 cc. could not be regarded as 1 R. U. The dosage was increased to 0.30 cc. in certain rats, including those that had given a — reaction to 0.25 cc. Of the 15 receiving the larger quantity, 11 gave a + reaction. Two of the other 4 on subsequent trial gave a + reaction with 0.30 cc., while 1 of the others gave a + reaction with 0.40 cc.; but the fourth gave a — reaction and required 0.50 cc. to show the typical cornified cells. It would be advisable to discard rats as irregular as the last two mentioned.

It seems, then, from these series of experiments, that in spite of our precautions to secure uniformity, about 20 per cent of the animals will be somewhat irregular in their response to injections of the ovarian hormone. By the injection of a standard stock solution, those rats which respond too easily or with too much difficulty may be eliminated. In effect, a standardization of the rats is carried out before they are used for routine standardization of unknown preparations. We have been following this procedure for some time. Notwithstanding this precaution, it is probably better to adopt Laqueur's (1927) idea that the volume which suffices to produce a + reaction in 75 per cent of the animals be regarded as 1 unit. For rough work a few animals suffice, but for more accurate assays it is advisable to use a considerable number in arriving at the final unitage.

Period of Serviceability of Test Animals: After using 19 of the test rats for weekly tests for a three months' period, they were again injected with 0.27 cc. of preparation No. 15578. Though these animals had increased considerably in weight, all gave a positive reaction; in fact, 14 gave + and 5 the ±±±. Two months later, *i. e.,* five months after spaying, 5 animals were tested with 0.27 cc. and 0.15 cc. With the first dosage all were +, with the latter all were —.

Table II contains the results of tests conducted after six and seven months' use of some of the test animals employed in obtaining the data of Table I. Of the 22 rats used, all gave a positive response to 0.27 cc., and 19 of the 22 gave at least the ±± to 0.15 cc. Of the three that were negative, one, No. 397, had required approximately 2 R. U. six months earlier, before a positive smear was obtained.

The interpretation to be placed upon Table II is that after prolonged use for testing, the animals become more sensitive and respond to smaller doses. Such a condition would, of course, introduce irregularities which increase the difficulty and decrease the accuracy of the assays. Our evidence, though limited in amount, indicates that the animals do not show an increase in sensitivity during the first five months of use. To be on the safe side, it might be well to use the animals only four months, *i. e.,* for 16 to 18 weekly tests.

Regeneration: The regeneration of ovarian tissue to which attention has been called by Davenport (1925) and Parkes, Fielding and Brambell (1927) might be a source of annoyance and uncertainty in assaying ovarian preparations. Parkes and his coworkers found that regeneration occured in only 11 out of 121 ovariectomized mice, but Davenport found a larger proportion in a series of animals in which the capsules and tubes were not removed.

As already stated, we have removed the ovaries with the periovarial fat, the fallopian tube and part of the uterus. In a series of 30 of the rats used in obtaining the data of Table I, and then subsequently for routine assays for a period of 5 or 6 months, no ovarian tissue was found at autopsy. Furthermore, though daily vaginal examinations were made, no oestrus or pro-oestrous smears were detected, except those at the normal time interval, after the injection of an active extract. During the

TABLE I
RESPONSES OF OVARIECTOMIZED TEST ANIMALS

Rat No.	*Volume Injected—Results of Tests		
	0.15 cc.	0.27 cc.	0.35 cc.
345	±	± ± ±	
346	−	+	
347	−	+	
348	−	+	
349	−	+	
350	−	+	
351	−	+	
352	−	+	
353	−	+	
354	−	+	
355	−	+	
356	±	+	
357	−	+	± ±
358	−	−	−
	(0.45 cc. +)		+
359	± ±		
	± ± ±		(0.21 cc. +)
	± ± ±		(0.10 cc. −)
360	−	+	
361	−	+	+
362	±	± ±	
363	± ±		(0.18 cc. ± ±)
			(0.21 cc. ± ± ±)
	±		(0.10 cc. −)
364	−	+	
365	−	+	
366	−	+	
367	−	±	
		± ±	
369	±	±	
		±	± ± ±
		± ±	
370	−	+	

Rat No.	**Volume Injected—Results of Tests		
	0.13 cc.	0.18 cc.	0.24 cc.
368	−	±	± ±
371	−	−	± ±
372	−	±	± ± ±
373	−	±	± ±
374		−	
375		±	+
376		−	± ±
377		−	+
378		± ±	+
379		−	
380		−	
	0.15 cc.	0.25 cc.	0.30 cc.***
374	−	+	
		± ±	
375	± ± ±	(0.17 cc. −)	
	−		
376	−	±	± ± ±
377	±	±	
378	−	±	± ±
379		+ +	
380	±	±	± ±
381	−	± ± ± ±	
382	−	± ± ± ± ±	
383	−	± ± ± ± ±	
384	−	± ±	± ±
385	+ −	± ± ± ±	
386	−	± ±	± ±
387	± ± −	+ +	
388	−	± ±	− (0.40 cc. ± ±)
389		−	− ± ± (0.40 cc. ± ± ±)
390		±	± ± ± (0.40 cc. +)
	0.17 cc.		
391	−	± ± ±	± ±
392	−	± ±	+
393	−	± ± ±	± ± ±
394	−	±	± ±
395	−	±	± ±
396	−	± ±	± ±
397		±	− (0.40 cc. − −)
			(0.50 cc. ± ± ±)

* Preparation No. 15578. ** Preparation No. 34072. *** Preparation No. 30540.

two weeks prior to autopsy, vaginal smears were made daily, but in this period no injections were made. Two smears were obtained which had an unusual number of epithelial cells for a dioestrous period. Dr. W. D. Collier of the Pathology Department kindly made a detailed histological examination of the region of the ovary, but was unable to detect any ovarian tissue.

Though the number of animals included in this study is somewhat limited, it seems safe to conclude that regeneration of ovarian tissue is not common in rats. In our experience during the past five years, the occurrence of oestrous or pro-oestrous smears at unexpected times has been very rare. It is improbable, then, that regeneration can cause much trouble in assay work, if the rats have been carefully ovariectomized.

PROPOSALS REGARDING TECHNIC OF STANDARDIZATION

1. Make daily smears for a two or three weeks' period before ovariectomy. Only those animals with normal cycles should be used.

TABLE II

RESPONSE OF TEST ANIMALS AFTER A PROLONGED PERIOD OF USE

Rat No.	Volume Injected Results of Tests		Rat No.	Volume Injected Results of Tests	
	0.15 cc.	0.27 cc.		0.15 cc.	0.27 cc.
354	+	+	389	± ±	+
358	± ±	+	390	± ±	+
360	± ±	+	391	± ±	+
363	± ± ±	+	392	±	+
364	+	+	393	± ±	+
381	± ±	+	394	−	± ±
382	+	+	395	± ±	+
383	+	+	396	+	+
384	+	± ± ±	397	−	+
385	±	+			
386	± ± ±	+			
387	+	+			
388	± ±	± ±			
After 6 months use			After 7 months use		

2. Make daily smears for two weeks after operation but before the beginning of injections. Discard any animal showing oestrous or pro-oestrous smears later than the second day after operation.

3. Prime the animals with 2 R. U.

4. One week later test the reaction of each animal by the injection of 1.3 R. U. If the smears are negative, discard the animal.

5. A week later test the reaction to 0.70 R. U.; if positive smears occur, discard the animal.

6. Use each animal for no longer than four months.

7. In attempting accurate assays, prime all animals by injecting 1.5 R. U., if the reaction of the preceding week was negative.

8. Use a sufficient number of animals. If 75 per cent of the animals injected with the same volume give a + reaction, consider that the amount injected contained 1 R. U.

BIBLIOGRAPHY

Allen, E. and E. A. Doisy: J. Am. M. Ass. **81**: 819. 1923.
Coward, K. H. and J. H. Burn: J. Physiol. **63**: 270. 1927.
Davenport, C. B.: J. Exper. Zool. **42**: 1. 1925.
Evans, H. M.: J. Biol. Chem. **77**: 651. 1928.
Evans, H. M. and Katherine S. Bishop: Anat. Rec. **23**: 17. 1922.
Evans, H. M. and G. O. Burr: Am. J. Physiol. **77**: 518. 1926.
Laqueur, E.: Münch. med. Wchnschr. **74**: 2045. 1927.
Laqueur, E., P. C. Hart, S. E. DeJongh and J. A. Wijsenbeek: Deutsch. med. Wchnschr. **52**: 4. 1926.
Loewe, S. and F. Lange: Ibid. **52**: 1286. 1926.
Parkes, A. S., U. Fielding and F. W. R. Brambell: Proc. Roy. Soc. **101 B**: 328. 1927.
Zondek, B.: Klin. Wchnschr. **5**: 1218. 1926.
Zondek, B. and S. Aschheim: Klin. Wchnschr. **5**: 979. 1926.

THE DISTRIBUTION OF THE OVARIAN HORMONE BETWEEN LIQUOR FOLLICULI AND THE RESIDUAL TISSUE*

SIDNEY THAYER AND EDWARD A. DOISY

From the Laboratory of Biological Chemistry, St. Louis University School of Medicine

ST. LOUIS

Although the work of Allen and Doisy and their collaborators has emphasized the importance of the Graafian follicle in the production of the oestrous hormone, no clear data regarding the amount of hormone that can be extracted from the liquor folliculi and the residual tissue have been published. To be sure, the results of a few random tests (Doisy, Ralls, Allen and Johnston, 1924,) have been cited, but no systematic report has been made. The English investigators (Dickens, Dodds, and Wright, 1925; Parkes and Bellerby, 1926,) have studied the distribution of the hormone between the follicular fluid and the residual tissue, and have published figures which indicate a more or less uniform distribution. They have concluded that the importance of the follicle has been unduly emphasized. To ascertain whether their position or the view expressed by Allen and Doisy is correct, we have undertaken the extraction of ten samples of liquor folliculi and the residual tissue from which the juice was obtained.

Fresh ovaries from the morning slaughtering were obtained from the chill room of the packing plant about 11:00 a. m. They were selected in that only those with apparently normal, ripe follicles were used. The liquor was aspirated from the ripe follicles and from others of size sufficient to contain appreciable quantities of liquor folliculi. The fluid was preserved with two volumes of 95 per cent alcohol, while the residual tissue was rinsed with water, passed through a meat chopper and mixed with twice its weight of alcohol.

*This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association. The authors take this opportunity to express their appreciation of this assistance.

The extraction of the liquor folliculi was carried out as described by Ralls, Jordan and Doisy (1926), but the purification with petroleum ether was omitted. The residual tissue was extracted by the procedure used in earlier work from this laboratory (Doisy, Ralls, Allen and Johnston, 1924). Care was taken to avoid the destructive effects of peroxides in the solvents used. Aliquots of the final extracts were distilled and the residue taken up in olive oil for the injections.

DISCUSSION

Data from the extraction of ten consecutive samples of liquor folliculi and residual tissue are available for discussion. An examination of Table I shows that the concentration of ovarian hormone in the liquor folliculi is much greater than in the residual tissue. It is significant that our results are in accord with the earlier work of Doisy and his associates (1924), but are contrary to the findings of Dickens, Dodds, and Wright (1925) and Parkes and Bellerby (1926). The English investigators, however, state that the follicles from which the fluid was obtained were not always large, since ovaries were seldom obtained from animals in oestrus. Doisy, Ralls, Allen and Johnston (1924) obtained between 220 to 2,000 rat units per kgm. of pig liquor from large follicles, with the average value falling about 450. (In a later work the average of 12 preparations was about 900 R. U.) Less than 200 units per kgm. were obtained from ovaries from which the liquor folliculi had been removed. These earlier findings are in agreement with our results. We obtained 690 to 1,228 rat units per kgm. of hog liquor, with the average value of 933, in contrast to the corresponding residual tissue, which gave from 124 to 199 rat units per kgm, with the average value of 167.

If one chooses to neglect the conception of concentration and merely considers the content of hormone in the two fractions of the ovary, our figures show almost twice as much in the liquor folliculi as in the residual tissue. The average for the 10 experiments are 304 and 187 rat units respectively. It must, of course, be realized that these figures are not absolute because of the impossibility of removing all of the follicular tissue. Many small follicles present in the ovaries were not aspirated, and con-

sequently contributed an uncertain amount of hormone to the residual tissue fraction. Zondek (1926) has found by his implantation procedure that the follicle wall contains sufficient hormone to produce oestrous in the spayed mouse. This quota of hormone would also appear in the residual tissue yield in our work. Considering both sources of error, it seems probable that our data for the residual tissue may be considerably too high and the figures for the liquor folliculi correspondingly low.

One experiment was carried out with cow ovaries. The corpora lutea were carefully dissected out, the liquor folliculi aspirated and the residual tissue treated by the same procedure used with the hog ovaries. The rat units per kgm. of tissue were: Corpora lutea 8, residual tissue 99, and liquor folliculi 613. These results do not agree with the findings of Parkes and Bellerby (1926), who state that the liquor folliculi from cow ovaries contains more hormone than the liquor folliculi from the hog. However, upon another point our findings are in accord with theirs, in that the amount of hormone of the residual tissue of hog ovaries is almost double that of cow ovaries. These data may be correlated with the fact that it is impossible to remove all the liquor folliculi from hog ovaries because a large number of small follicles are distributed throughout the ovary, whereas cow ovaries generally have only a few large follicles, since as a rule but one follicle ripens at each oestrous.

There seem to be two possible explanations of the differences of our results from those of Parkes and Bellerby. 1. The ovaries used by the English investigators may have been mainly in the dioestrous stage, and therefore, according to our view, contained only a small quantity of the hormone. The ovaries used in our work were carefully selected and only those with large, normal follicles used. Approximately one-fourth of the weight of the ovaries was liquor folliculi. 2. The method of extraction may possibly have caused the low yields obtained by Parkes and Bellerby. In a recent paper (Thayer, Jordan and Doisy, 1928,) we have shown that peroxides present in ethyl ether may produce serious losses of activity of the ovarian hormone, and that the more refined a preparation is the more readily oxidation occurs. The liquor folliculi extracts are much purer than extracts of the residual tissue, and therefore may suffer greater losses.

SUMMARY

1. The observations of ten experiments support the view of the importance of the Graafian follicle in the production of the oestrous hormone.

2. The average number of rat units per kilogram from liquor folliculi is 933 and from residual tissue 167.

TABLE I

COMPARISON OF LIQUOR FOLLICULI AND RESIDUAL TISSUE

Preparation No.	Residual Tissue			Liquor Folliculi		
	Weight	Total Yield	Yield per Kilo	Weight	Total Yield	Yield per Kilo
	Grams	Rat Units	Rat Units	Grams	Rat Units	Rat Units
3A	2264	323	142	517	430	830
7A	1057	211	198	312	312	998
8A	1031	206	199	309	309	988
9A	854	106	124	262	218	830
10A	789	112	141	324	203	690
11A	1049	139	132	352	293	820
12A	1276	255	198	365	455	1228
13A	1092	156	142	317	317	982
14A	907	181	199	265	265	980
15A	922	184	198	240	240	984
Average....	1124	187	167	326	304	933

BIBLIOGRAPHY

Allen, E. and E. A. Doisy: J. Am. M. Ass. **81:** 819. 1923.
Dickens, F., E. C. Dodds and S. Wright: Biochem. J. **19:** 853. 1925.
Doisy, E. A., J. O. Ralls, E. Allen and C. G. Johnston: J. Biol. Chem, **61:** 711. 1924.
Parkes, A. S. and C. W. Bellerby: J. Physiol. **61:** 562. 1926.
Ralls, J. O., C. N. Jordan and E. A. Doisy: J. Biol. Chem. **69:** 357. 1926.
Thayer, S., C. N. Jordan and E. A. Doisy: J. Biol. Chem. In press.
Zondek, B.: Klin. Wchnschr. **5:** 1218. 1926.

THE THYROID GLAND IN INFECTIONS; THE EFFECT UPON THE BASAL METABOLIC RATE*

N. A. WOMACK, M. D., W. H. COLE, M. D., AND
A. G. HEIDEMAN, M. D.

Department of Surgery, Washington University School of Medicine and the Barnes Hospital

ST. LOUIS

The fact that the thyroid gland plays a very important role in the growth of an animal and in the regulation of the body metabolism has been recognized for some time. In a recent communication (1) we called attention to the fact that in cer-

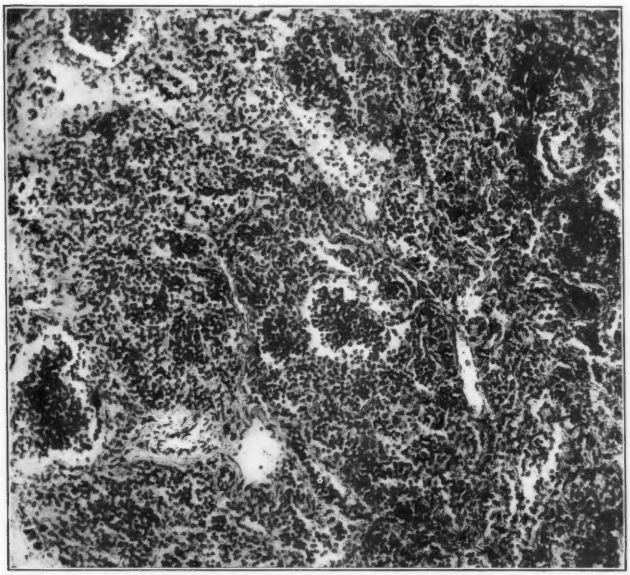


Fig. 1. Section from the thyroid gland of a dog dying of intestinal obstruction. The normal architecture of the gland has been changed by the desquamation, hyperplasia and loss of colloid. The remnants of a few acini may still be seen.

*Read before the Twelfth Annual Meeting of the Association for the Study of Internal Secretions, Minneapolis, June 12, 1928.

tain systemic infections and in severe toxemias very definite chemical as well as histological changes in the thyroid gland could be demonstrated. These changes varied considerably with the severity of the infection. Microscopically we were able to show that in the more virulent infections there was desquamation and death of many of the acinous cells, loss of colloid and hyperplasia of many of the remaining cells. This resulted in a marked change in the normal architecture of the gland (Fig. 1). There was a concomitant enlargement of the gland. Upon chemical analysis, however, the iodine content per gram of tissue was found to be about half the amount found in the thyroid glands of the control animals.

Such facts are not surprising when one considers the important part the thyroid plays in the metabolism of the body. It has long been an established fact that in infections there is an increase in metabolism. More recently calorimetric studies of the increase in heat production have been made by Barr and Du Bois in malaria (2), Coleman and Du Bois in typhoid fever (3) and McCann and Barr in tuberculosis (4). Likewise it has been found by Schick, Cohen and Beck (5) that during convalescence after pneumonia the basal metabolic rate is often lower than normal. They found this true in other diseases associated with a low pulse rate during convalescence (6). During the febrile stage of an infection a definite relationship between the rise in fever and the rise in metabolism has been noted by Du Bois (7) which conforms roughly to the law of physical chemistry first suggested by Van't Hoff, i.e.: "With a rise in temperature of 10 degrees, Centigrade, the velocity of chemical reactions increases between two and three times" (8). This relationship, however, is subject to some variation probably depending to a certain extent upon the differences in the level of protein metabolism maintained in different diseases.

With these facts in mind we have studied the effects of experimentally produced infections in animals on the basal metabolism and the changes produced following the administration of iodine. We have also noted definite changes in the clinical course of these infections as well as in the chemical and histological structure of the thyroid gland.

METHOD

The apparatus used for the determination of the basal metabolism consisted of a closed respiratory chamber of the Benedict type to which a specially devised mask was attached. This mask was made of a small can to which was attached a rubber sleeve that fit snugly over the dog's muzzle. If a rubber dam bandage was first wrapped around the dog's head at the level of the eyes it was found that this apparatus was perfectly airtight and apparently comfortable. Encircling the fingers around the rubber sleeve at the dog's muzzle is strongly advised to prevent leakage at this point. The dogs used in these experiments were kept on a standard diet consisting for a large part of cooked meat, care being taken to avoid any food that might contain iodine. Before the experiment was begun a small amount of thyroid tissue was removed for microscopic examination, not enough, however, to be a factor in producing subsequent hyperplasia of the gland. After recovery from the biopsy the animals were trained to lie perfectly quiet and relaxed on a table while the metabolism tests were being run. This seemingly difficult part of the procedure was accomplished with surprising ease. Usually after five or six attempts the animal would remain quiet throughout the entire test and uniform readings could be obtained.

A real difficulty, however, was encountered in the computation of the surface area. The generally used Du Bois height-weight formula was naturally inapplicable. Because of the marked variation in shape any surface area formula based on the weight alone is inaccurate when applied to dogs. It would seem, however, that the important fact is the determination of the normal metabolic level of the particular animal under experimentation rather than using a standard factor. Kunde and Steinhaus (9), by using dogs of comparatively the same weight, obtained an average basal metabolism for normal dogs of 771.2 calories per square meter per 24 hours. Meeh's formula was used in their work. Boothby and Sandiford (10) quote a somewhat higher average. The surface area formula used by us was $0.103\sqrt[3]{wt^2}$. As might be expected, there was considerable variation in those dogs of extreme weights. Our average for

19 normal dogs was 885.21 calories per square meter per 24 hours.

In these experiments 19 dogs were used. Of this number 7 were fed iodine in the form of Lugol's solution, 2 were fed thyroid extract and 10 were used as controls. The Lugol's solution was masked in the food; the dose used was one minim per kgm. of body weight. The iodine feedings were begun several days before the infections were produced and continued through-

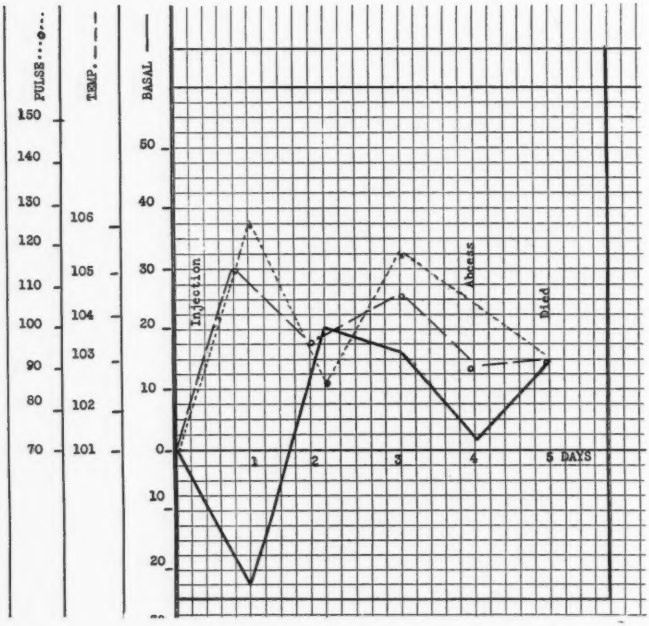


Chart 1. Basal metabolism, pulse and temperature of a dog that died 5 days after the injection of 0.8 cc. of toxin per kgm. of body weight. Note the initial drop in metabolism below normal. The subsequent rise is not as great as is usually seen, suggesting a depression of oxygen consumption. The pulse rate is unusually high.

out the experiment. A few infections were produced by ligation of the appendix. The majority, however, were produced by the injection of a toxin consisting of the contents of a strangulated loop of gut. Upon culture it was found also to contain Hemolytic Streptococcus, B. Welchii, B. Coli, and B. Proteus.

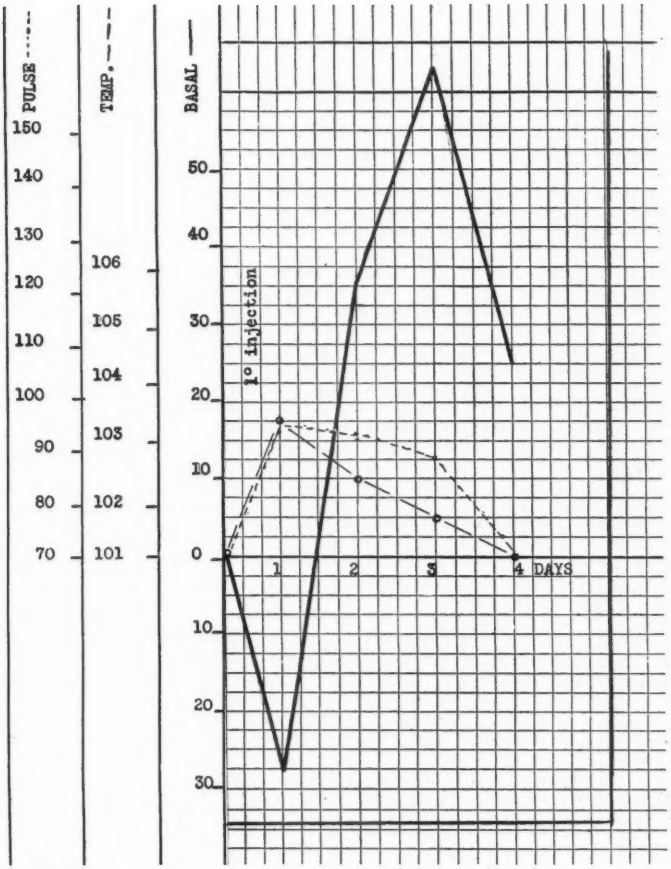


Chart 2. This chart shows the initial depression in metabolism following the injection of toxin with a subsequent high rise. This animal was not fed iodine.

The amount used was eight-tenths of a cubic centimeter per kgm. of body weight and both control animal and the animal that had been fed iodine were injected at the same time in order to avoid any daily variation in the strength of the toxin.

As soon as several consistently low basal metabolism readings had been obtained the animals were injected with the toxin

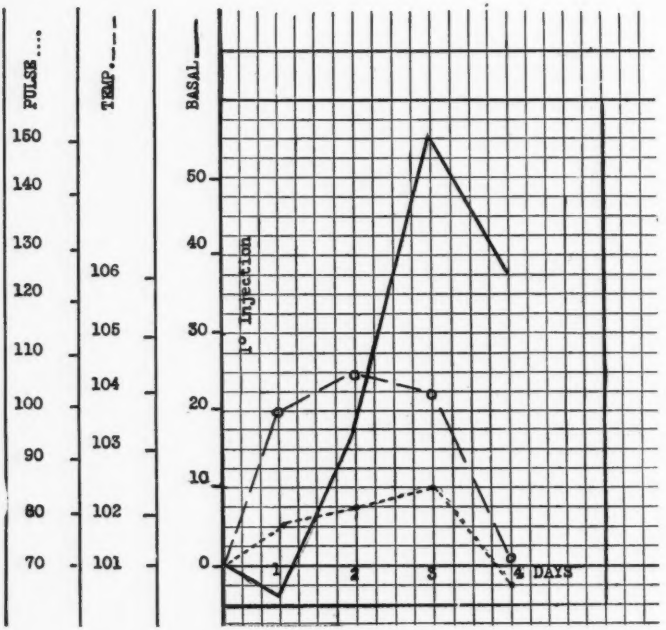


Chart 3. This dog received iodine before and during his infection. Note the absence of the depression phase and the failure of the basal metabolism to rise subsequently as high as in the control dog shown in Chart 2.

subcutaneously with comparatively little discomfort. Daily basal metabolism readings were then made until the animals died or began to recover from their infections. Those animals that recovered were then given larger doses to determine if there was any variation in the resistance of those that had been fed iodine and the control dogs.

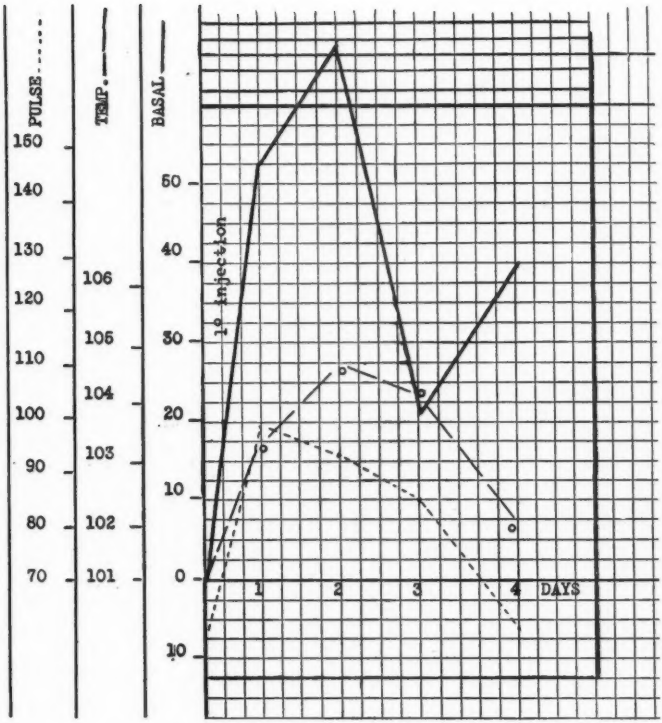


Chart 4. Control dog—without iodine. Note the lack of initial depression, with high immediate rise in metabolism. This animal was not as sick as those shown in Charts 1 and 2. See Fig. 2 for the microscopic picture of the gland in this dog.

DISCUSSION

If the infection was so fulminant in character that the animal died within twenty-four to thirty-six hours there was noted a drop in oxygen consumption below normal which persisted. If, however, the infection was not quite so severe, there was seen an initial drop in basal metabolism below normal which

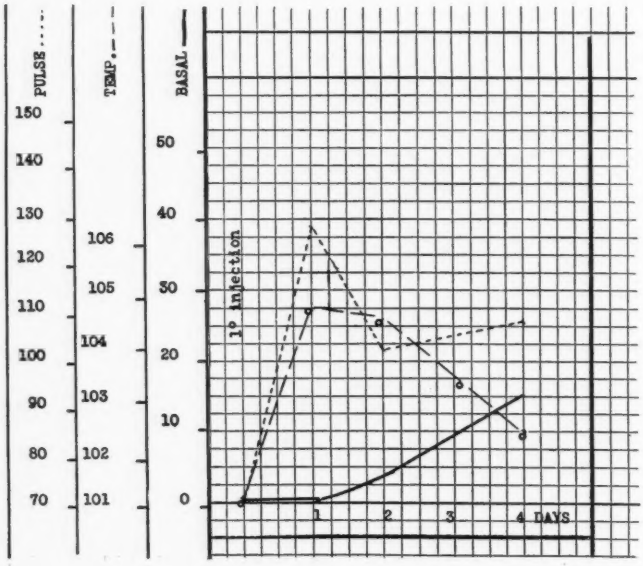


Chart 5. The basal metabolism curve of dog fed iodine during the experiment. Note the comparatively slight rise in basal metabolism. Compare with control animal shown in Chart 4. Section from the thyroid of this dog is seen in Fig. 3.

soon rose to well above normal where it persisted until the animal recovered (Charts 1 and 2). In still less severe infections the initial drop was not seen, the basal metabolism rising to well above normal but not as high as in the preceding group of cases (Charts 4, 6 and 8).

In those animals that were fed iodine the basal metabolism was consistently lower than in the control cases with the exception of the very severe cases in which the control dogs showed

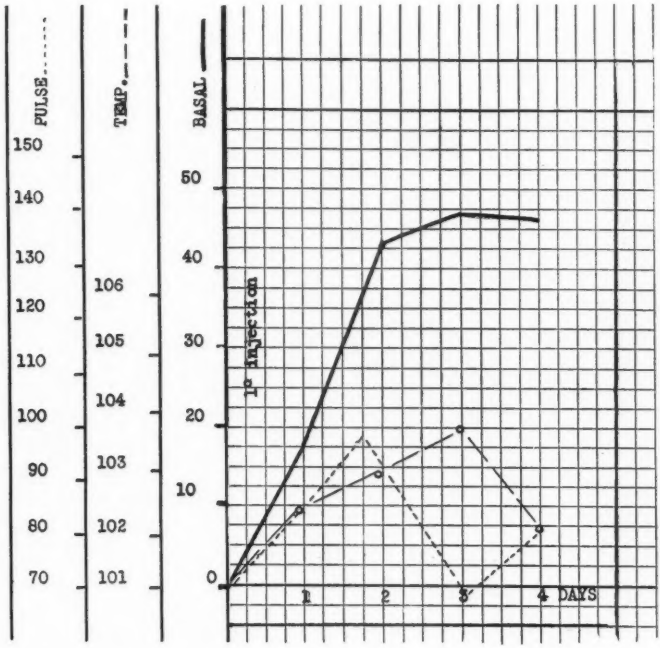


Chart 6. Basal metabolism of dog not fed iodine. Compare with Chart 7.

a depression of oxygen consumption. Here the readings were higher (Charts 3, 5, 7 and 9). In general the temperature and pulse rate were perhaps lower in the iodine dogs but not as low as one would expect when considering the very marked effect on the pulse rate in exophthalmic goiters. Practically all of the dogs that were fed iodine showed clinical improvement before the control dogs. Neither was the immediate reaction so

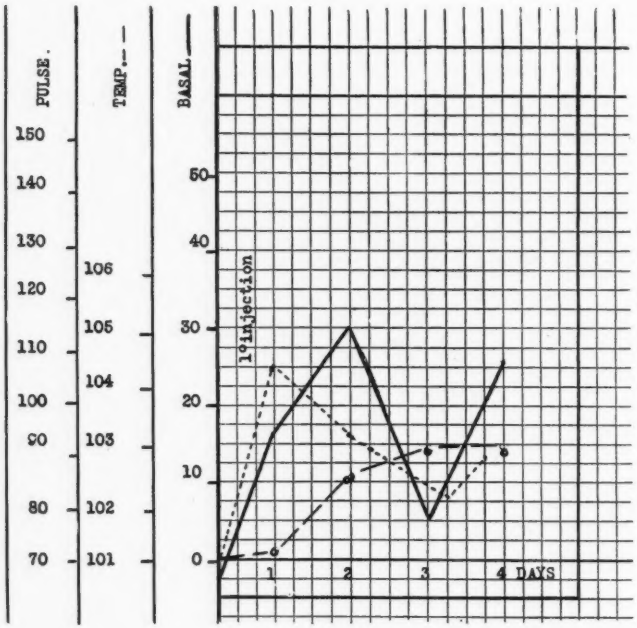


Chart 7. Basal metabolism of dog fed iodine during the experiment. Compare the lowered oxygen consumption with the control animal shown in Chart 6.

severe. None of the iodine dogs died following the injections, while two of the control dogs died. Following ligation of the appendix one control dog, one dog that had been fed iodine and one dog that had received thyroid extract died. These latter two animals lived over fifty hours, while the control animal lived about thirty hours.

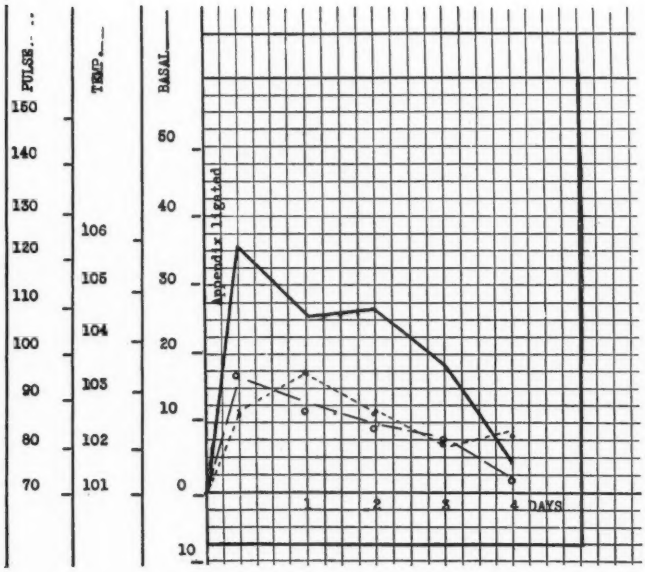


Chart 8. Reaction following the ligation of the appendix in a dog not fed iodine.

Histologically the hyperplasia and desquamation so often seen in the thyroid gland of animals with severe infections were absent in those glands that had received iodine (Figs. 2 and 3). Likewise the latter group of glands often contained as much as two or three times the amount of iodine seen in the normal thyroid of a dog. The dogs receiving thyroid extract showed similar changes to those dogs receiving iodine but not quite so marked.

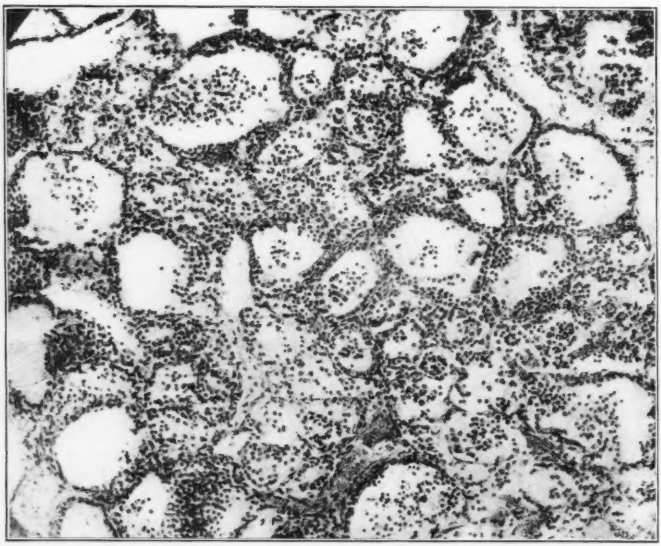


Fig. 2. Section from the thyroid of a dog following the injection of toxic material as described in the text. The basal metabolism curve is shown in Chart IV. Here one sees desquamation, deficiency of colloid and beginning of hyperplasia. Many of the cells are columnar in type.

That such changes as described above cannot be explained on the basis of hyperpyrexia alone can be shown by the fact that similar changes in the metabolic rate and structural and chemical changes in the thyroid gland may be produced by the injection of a toxin such as histamine without the production of fever (Chart 10, Fig. 4).

As Farrant (11) has shown, certain organisms are more prone to produce the structural changes in the thyroid gland than others. It is probable that infections produced by such organisms are those that are associated with a high level of protein katabolism. Those conditions such as chronic tuberculosis (4) and chronic bacterial endocarditis, in which protein metabolism is relatively low, produce a relatively lower rise in basal metabolism and show considerably less structural change

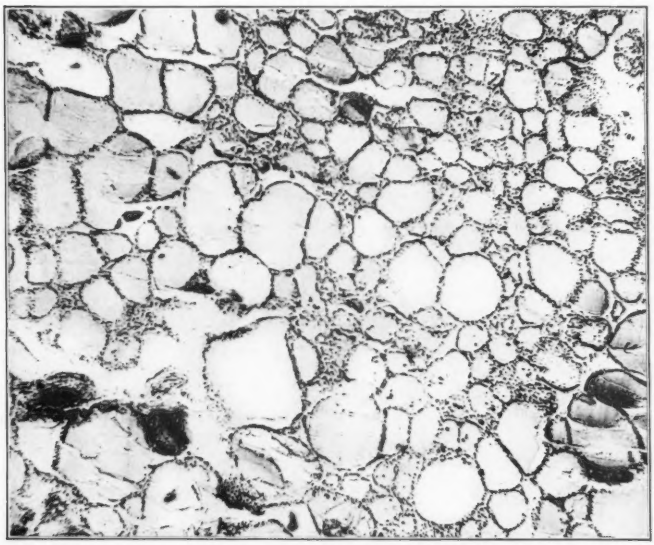


Fig. 3. Section from the thyroid of a dog, the basal metabolism curve of which is shown in Chart V. This animal was injected with toxin, but received iodine before and during the experiment. Note the practically normal appearance of the gland. Compare with Fig. 2, the control animal for this experiment. This gland contained several times the normal amount of iodine, while that shown in Fig. 2 contained much less than is found in the normal gland.

in the thyroid gland. Generalized peritonitis on the contrary produced extensive changes in the thyroid gland (12).

Usually there is no great change in the respiratory quotient during infections, suggesting a fairly normal fat and carbohydrate metabolism. The idea that we are dealing chiefly with the effects of protein metabolism is strengthened when we consider that heat production is increased through the specific dy-

namic action of proteins. That this specific dynamic action could be produced by the feeding of component amino acids has been shown by Lusk (13), and more recently by Wilhelmj and Bollman (14) by intravenous injections of certain amino acids. We have been able to produce similar changes in the thyroid gland to those described above by the repeated injections of large amounts of glycocoll subcutaneously sufficient to cause

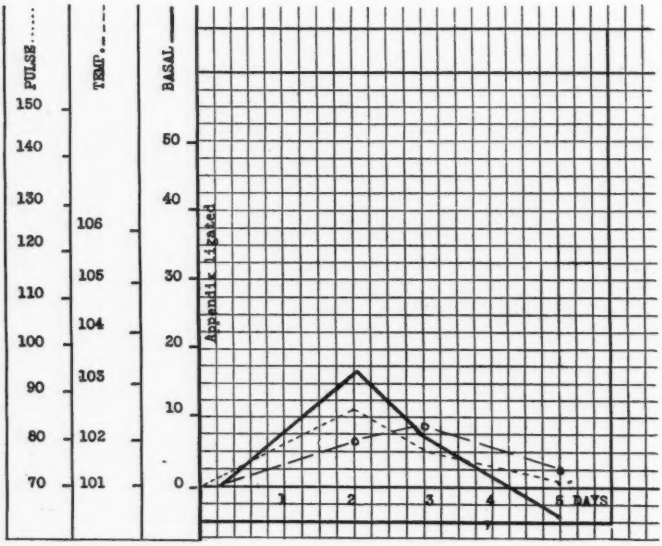


Chart 9. Reaction following the ligation of the appendix in a dog fed iodine. Note the reduction in the basal metabolic level. Compare with Chart 8, the control.

death (Fig. 5). It has been shown (14) that this amino acid has a fairly high specific dynamic action. That the thyroid may be involved in the specific dynamic action of proteins is not a new idea. Baumann and Hunt (15) have demonstrated that there is a gradual disappearance of this phenomenon following the complete removal of the thyroids of rabbits. Incomplete thyroidectomy showed only a decrease in the specific dynamic

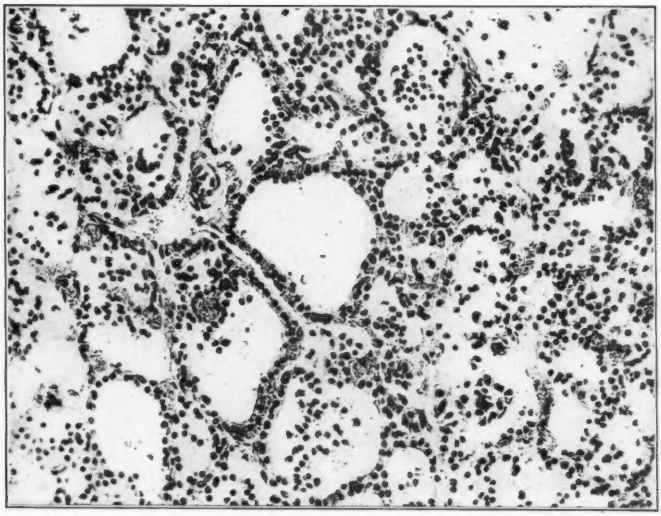


Fig. 4. Changes in the gland of an animal that received subcutaneous injections of histamine. Note the same changes as seen in Fig. 2. See Chart X.

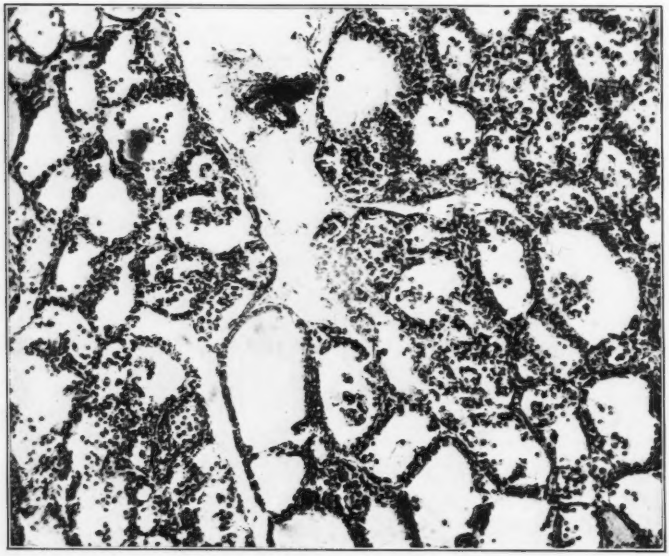


Fig. 5. Changes in the thyroid gland of a dog which was given glycocoll subcutaneously. This animal was given 1 gram per kgm. of body weight on the first day, 2 grams on the second day, and 2.5 grams on the third day. The changes here resemble those seen in Fig. 4.

action that could be returned to normal by the administration of potassium iodide.

The mechanism by which these changes are produced is not easily explained. It could possibly be a direct toxic action on the thyroid parenchyma. If this were true one would expect to find a similar destruction in other parenchymatous organs.

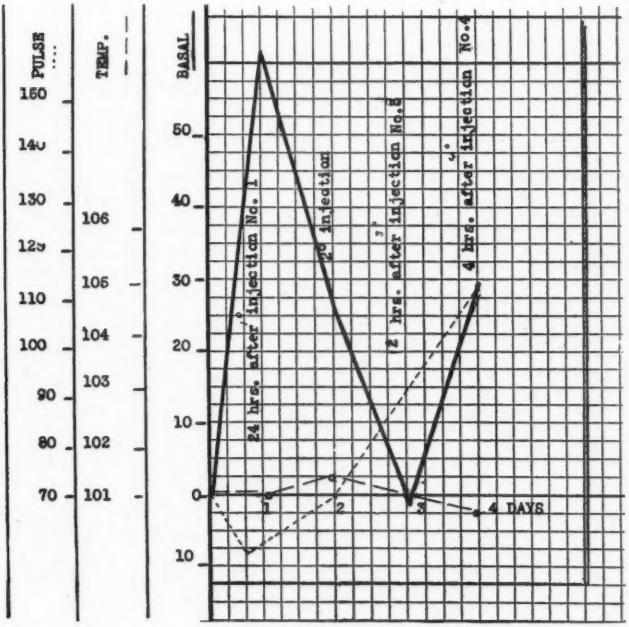


Chart 10. Basal metabolic curve, pulse and temperature of dog following the injection of histamine. Dog sacrificed on the 5th day. There is practically no rise in temperature. The metabolism is at its highest 24 hours after injection. The 2nd reading, taken 36 hours after the first injection and just before 2nd injection, shows a beginning fall. The third reading, taken 2 hours after the 3d injection, shows no rise. This may possibly be interpreted as a depression in oxygen consumption immediately following the injection of histamine. The 4th injection shows a beginning rise. See Fig. 4.

With the exception of a moderate amount of cloudy swelling and chronic passive congestion this was not noted. Furthermore, such a direct toxic action would not sufficiently explain the depletion of thyroid iodine. Hyperplasia, loss of colloid

and even death of the acinous cells could be explained by stimulation of the thyroid gland even to the point of exhaustion by demand of the somatic cells upon the thyroid for its catalytic secretion. It is an interesting fact that the feeding of iodine during such periods of strain lowers the basal metabolism and produces an entirely different picture in the structure of the thyroid gland.

SUMMARY

Characteristic microscopic and chemical changes have been produced in the thyroid glands of dogs by the experimental production of infections and toxemias. These changes have been associated with a rise in basal metabolism.

The feeding of iodine has tended to prevent the above changes and lower the basal metabolism.

BIBLIOGRAPHY

1. Cole, W. H. and N. A. Womack. The thyroid in infections. J. A. M. A. **90:** 1274. 1928.
2. Barr, D. P. and E. F. Du Bois. Clinical calorimetry, twenty-eighth paper. The metabolism in malarial fever. Arch. Int. Med. **21:** 627. 1918.
3. Coleman, Warren and E. F. DuBois. Clinical calorimetry, seventh paper. Calorimetric observations on the metabolism of typhoid patients with and without food. Arch. Int. Med. **15:** 887. 1915.
4. McCann, W. S. and D. P. Barr. Clinical calorimetry, twenty-ninth paper. The metabolism in tuberculosis. Arch. Int. Med. **26:** 663. 1920.
5. Schick, B., P. Cohen and Isabelle Beck. Basal metabolism after pneumonia. Am. J. Dis. Child. **31:** 228. 1926.
6. Schick, B. and P. Cohen. Lowered basal metabolism in post-infectious stages and diseases characterized by slow pulse rate. Preliminary report, Am. J. Dis. Child. **30:** 291. 1925.
7. Du Bois, E. F. The basal metabolism in fever. J. A. M. A. **77:** 352. 1921.
8. Van't Hoff, J. H. Studies in chemical dynamics, Revised by E. Cohen, Translated by T. Ewan. Easton, Pa., Chemical Publishing Co., 1896. (Quoted by Du Bois, ibid.)
9. Kunde, Margaret and A. H. Steinhaus. Basal metabolism of normal dogs. Am. J. Physiol. **78:** 127. 1926.
10. Boothy, W. and I. Sandiford. The calorigenic action of adrenalin chloride. Am. J. Physiol. **63:** 407; **66:** 93. 1923.
11. Farrant, R. The pathological changes of the thyroid in disease. Brit. M. J. 470. 1914.
12. Cole, W. H., N. A. Womack and S. H. Gray. The thyroid in infections and toxemias. Changes in human glands. (Paper to be published.)
13. Lusk, G. Animal calorimetry, fifth paper. The influence of the ingestion of amino-acids upon metabolism. J. Biol. Chem. **13:** 155. 1912-1913.
14. Wilhelmj, C. M. and J. L. Bollman. The specific dynamic action and nitrogen elimination following intravenous administration of various amino-acids. J. Biol. Chem. **77:** 127. 1928.
15. Baumann, E. J. and Louise Hunt. On the relation of thyroid secretion to specific dynamic action. J. Biol. Chem. **64:** 709. 1925.

PINEAL AND METAMORPHOSIS
THE INFLUENCE OF PINEAL FEEDING UPON THE RATE OF METAMORPHOSIS IN FROGS

JOHN ADDAIR and F. E. CHIDESTER*
Department of Zoology, West Virginia University
MORGANTOWN, WEST VIRGINIA

Before taking up the discussion of the effect of pineal feeding on amphibians, it might be well to summarize the effect of pineal feeding on higher animals, as reported by different observers. Very little has been done in this field.

RESULTS OBTAINED FROM FEEDING OF PINEAL GLANDS

Dana and Berkeley (1913) find that feeding results in increased general growth development of genital organs and deposit of sub-cutaneous fat above normal in young guinea pigs, rabbits, and kittens.

McCord (1914-15) finds accelerated growth in chicks guinea pigs and puppies. Injections of pineal extract with guinea pigs showed increased rate of growth. McCord states that veal pineal has more marked effect than that of old cattle. Dogs fed pineal gland were one month ahead in mental development. Guinea pigs developed rapidly and bore young 14 days ahead of controls. Chickens fed on pineal from old cattle showed slow growth which was greatly accelerated by shifting them to veal pineal. McCord concludes that if pineal from young animals is fed in small amounts to young animals the body growth will be stimulated till normal growth is attained with only a moderate amount of precocity of mental and sexual development.

McCord (1915) further says that children mentally defective when treated with pineal extract do not show any acceleration of growth but do show mental improvement if treated before 15 years of age. The digestive juices of the stomach and intestine sometimes change the composition of gland extract.

*Aided by the G. W. Carnrick Company.

Intravenous pineal injections have shown, however, that pineal extract is not decomposed in the digestive process since the result in both cases has been the same.

Very little has been accomplished in the feeding of pineal to amphibians. The following is a brief summary of the findings in this field:

Adler (1914) in feeding tadpoles had 19 alive at end of 19 days. Three lived 82 days. No abnormality in sexual development was noted. None developed into frogs.

McCord and Allen (1917) find that beef pineal extracted with acetone if fed for 10 days causes transparency of tadpoles 45 minutes after feeding on account of contractions of the melanophores or pigment spots of the lower layer of the epidermis. This acetone extract does not greatly influence growth. Its residue, however, does, thus showing that there are two active principles in the pineal.

McCord (1917) finds that tadpoles fed for two weeks on pineal tissue are twice the size of controls and show no signs of differentiation. He finds that the ultimate differentiation is earlier, but that metamorphosis occurred in the controls also.

In reviewing the above data relative to the feeding of pineal to both amphibians and other vertebrates the following questions arise:

1. Will feeding of the gland to amphibians accelerate the rate of growth as in the case of higher animals?
2. Will deposits of fat result as in the case of higher animals?
3. Will there be an increase in size of the pineal fed individuals?
4. How do results obtained from pineal feeding compare with those obtained by thyroid feeding?
5. What other results are noted in connection with this experiment?

EXPERIMENTAL PROCEDURE

It was with these questions in mind that we began the experiment of feeding tadpoles pineal extract in connection with pork liver. In carrying out this work 54 tadpoles of Bufo americana were used. Feeding began on June 16, 1928 and ended on July 20, 1928. The animals were fed once each week as much liver as they could consume at one time and the remainder was removed in order to prevent poisoning by decay.

The pineal was in desiccated capsule form (½ grain pineal with ½ grain milk sugar) and was not mixed with the food at all but was simply placed in the water of the battery jars where the tadpoles were kept. Twelve hours after giving the pineal the water was changed as it would become slightly tinged with a translucent colloid substance and the tadpoles showed an abnormal disposition to remain motionless at the surface if the water was not changed.

Marked changes were noted in the appearance of the pineal fed individuals as early as a week after the first feeding. A clear, baglike membrane developed on the ventral side just anterior the pelvic region. The bulging ventral portion of the abdomen (which is characteristic of normal tadpoles) disappeared and the ventral surface became flattened. The dark pigmentation of the sides and tail disappeared, due no doubt as McCord states, to contractions of the melanophores. Except for some white, flaky granular material, the skin in these regions was almost transparent. The entire body outline became slimmer and more salamander-like in appearance than that of the controls. A sluggish condition for two days following each pineal feeding was noted. The controls on the other hand played and swam about in the lively manner of all normal tadpoles.

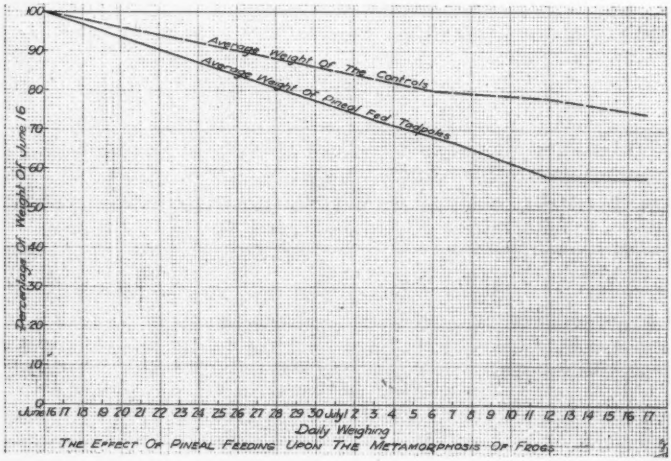
The rate of metamorphosis proceeded rapidly after the second feeding of pineal (July 1) as is shown in the record of development of the fore legs. Rapid absorption of the tail followed and many deaths resulted at that stage before final absorption of the tail. (The action of pineal at this point was similar to that of thyroid). It was also noted that death invariably resulted if individuals at the stage of development of the fore legs were given pineal. It soon became apparent that the dose of ½ grain pineal was too severe and as the death rate continued at these two stages of development, no pineal was given at all between the dates of July 1 and July 12.

The results of such discontinuance were almost immediate. No further deaths resulted and on July 11 one tadpole passed safely through the dangerous stage of tail absorption, became a frog and fed on insects. Two other tadpoles developed into frogs on the following day (July 12) and also fed on insects.

By July 13 it appeared that the effects of the pineal administered two weeks previously had run its course. No more

tadpoles developed fore legs. They regained the dark nomal pigmentation of the sides and tail and the abdomen became pouched and rounded more like that of the controls. The body volume also appeared to increase. It was clear that the effect of pineal—unlike that of thyroid—was on the wane and if discontinued entirely development would proceed along the same lines as that of the controls.

Accordingly, it was decided to give a dose of only ¼ grain pineal and attempt to start up development again. This was done on July 13 and the results were almost immediate, as is shown in the table of the development of fore legs. Three of the five that developed fore legs on July 15 died and two died on July 17 upon developing fore legs, thus showing that pineal, even in small doses, is very dangerous at this stage. The remainder of those fed on pineal again resumed the pale, washed-out appearance and the abdomen became flattened again as before.



THE EFFECT OF PINEAL FEEDING UPON THE METAMORPHOSIS OF FROGS

Contrary to the findings of Dana and Berkeley with mammals the feeding of pineal to amphibians results in a rapid loss of body weight. As has been said before, this is apparent to the eye of the casual observer. The average weights given below of

both pineal fed individuals and controls show that an enormous tearing down of body tissue results from pineal feeding.

AVERAGE WEIGHT OF TADPOLES

Date	*Pineal Fed*	*Controls*
June 16	2.674 grams.	2.674 grams.
July 6	1.817 grams.	2.14 grams.
July 12	1.54 grams.	2.075 grams.
July 17	1.55 grams.	1.98 grams.

The accompanying graph (see previous page) also affords a comparison in percentages as to the relative loss in weight in the controls and feeders.

The rate at which pineal hastens the development of fore legs may be seen by the following table:

II. Rate of Foreleg Development of Pineal Feeders.

(Pineal fed from June 16 to July 1 once each week.)

Date		
July 1	1	No pineal fed from July 1 to
5	1	July 12.
6	2	
8	2	
9	2	
10	1	
11	2	
12	0	Effects of pineal disappear-
13	0	ing here. One-fourth grain
14	0	pineal given on July 13.
15	5	Note immediate effect of re-
16	3	sumption of pineal dosage.
17	2	

SUMMARY

1. Pineal hastens the rate of metamorphosis, much in the same manner as thyroid does, but is not so powerful as thyroid in this respect. Furthermore, if the feeding of the pineal is discontinued, development slows up. Resumption of pineal feeding results in a sudden speeding up of the rate of metamorphosis.

2. Unlike the findings of McCord (1917) the pineal fed individuals lost weight rapidly while the weight of the controls more nearly remained constant.

3. Twenty-two pineal fed individuals developed fore legs and eight passed through the tail absorption stage into that of the adult form in the course of thirty-one days. No change whatever in the way of differentiation was noted in the controls.

BIBLIOGRAPHY

Dana, C. L., and W. N. Berkeley: 1913. Med. Rec. **83**: 835.
McCord, C. P.: 1914. Am. M. Ass. **63**: 232.
McCord, C. P.: 1915. Inter. Med. J. **22**: 354.
Adler: 1914. Arch. f. Entwckengsmch. **40**: 18.
McCord, C. P., and May Allen: 1917. J. Exper. Zool. **23**: 207.
McCord, C. P.: 1917. Surg. Gyn. & Obstet. **25**: 250.

A NOTE ON THE RELATION OF LIGHT TO THE ACTION OF PARATHYROID EXTRACT

HECTOR ROSELLO AND L. M. PETRILLO

From the Laboratory of Therapeutics, University (Medical School) of Montevideo

MONTEVIDEO

From the work of Hanson; Berman; Collip; Clark and Scott; Hjort, Robinson and Fendrick; Fisher and Lawson, the effect of acid extracts of parathyroid glands on the blood calcium is now well known. A rise in the blood calcium level above 17 mgm. per 100 cc. is dangerous to the life of the animal (according to Collip's and Salvesen's studies) leading to a sequence of symptoms of more or less gravity (diarrhea, etc.). If administration of the extract is continued the symptoms become more and more grave simultaneously with the augmentation of the calcemia.

Collip and Scott have observed that it is possible to induce a rapid rise of the blood calcium by injections of small quantities of the extract once or twice every day. Collip succeeded in some cases in making the calcium rise with 2 or 3 injections of 20 units each and to maintain it elevated for some time.

In our laboratory, aided by Dr. Bennatti and Miss E. Balet, we have confirmed the earlier work, using Parathormone (Lilly) and noting hypercalcemia, grave symptoms and, in continued experiments, death. Blood calcium was determined by the Tisdall-Kramer method as modified by Scott, centrifuging the fluid. The dogs on which we experimented weighed between 7 and 12 kgm. It is especially to be noted that during the experiments the dogs were kept in a dark cellar. The diet was invariably meat, milk, bread and water. But in these animals we observed that to be able to make the calcemia reach the higher levels, as rapidly as did Collip and others, we had to repeat the injections many times over a period of 8 to 10 days. The hypercalcemia thus secured decreased rapidly as soon as the injections were discontinued. The following table sets forth the details of one of our experiments:

Dog—8 kgm. normal.
December 6—Blood calcium..... 0.0105
December 6—Injected 20 units extract
December 7—20 + 20 units extract
December 8—20 + 20 units extract
December 8—Blood calcium..... 0.0132
December 9—20 + units extract
December 10—20 units extract
December 10—Blood calcium..... 0.0165
December 10—20 units extract
December 11—20 + units extract
December 12—20 + 20 units extract
December 13—20 units extract
December 13—Blood calcium..... 0.0177
December 14—None injected
December 15—20 units extract
December 15—Blood calcium..... 0.0150
December 16—20 units extract
December 16—Blood calcium..... 0.0108
December 17—Normal.

At first these meager results were attributed to lack of potency in the extract employed. But wishing to take a photograph of one of the animals on which we experimented, during the period of grave symptoms, we took the animal from the dark cellar to the laboratory, where he was for some time exposed to sunlight before a window. We observed, then, that his symptoms became rapidly more grave (more dyspnea and asthenia). When the same phenomena were noted in case of a second animal, we decided to investigate specifically the effect of light on the reactions.

A normal, white fox terrier dog, weighing 9 kgm., had blood calcium of 0.0098. He was kept in darkness throughout the experiment. He was given parathyroid extract subcutaneously in 20 unit doses, according to the following schedule:

December 5—20 units
December 6—20 units
December 7—20 units, blood calcium..... 0.0128
December 8—20 + 20 units
December 9—20 + units
December 10—20 units, blood calcium..... 0.0143
December 10—20 units
December 11—20 + 20 units
December 12—20 units, blood calcium..... 0.0150

At 4:30 p. m. the blood calcium was determined (0.0150). The animal was asthenic and dyspneic. He was then brought to the laboratory and exposed to sunlight for 45 minutes. His dyspnea and asthenia increased considerably and at 5:15 p. m. the blood calcium was 0.0157. He died during the night.

How much weight is to be ascribed to the 5 per cent increase in the blood calcium in this single case is, of course, doubtful, but the direction of the change upon exposure to light is certainly of interest. It would seem to correlate with the augmentation of calcium provoked by exposure to ultra violet light in case of rachitic and parathyroprivic subjects.

Further experiments of this nature have been prevented by lack of extract.

That sunlight has no influence upon the blood calcium of normal animals nor of non-treated parathyroprivic animals with hypocalcemia and tetany we have shown experimentally. Two characteristic cases may be cited.

A normal dog, weighing 9.500 kgm., was parathyroidectomized on March 3rd. The blood calcium at this time was 0.0097. On March 5th the animal was tetanic and the calcium had fallen to 0.0058. After exposure to sunlight for one hour the symptoms did not change and the blood calcium remained at 0.0056. Death occurred the following day.

A normal dog, weighing 8 kgm., was kept in darkness for 8 days. The initial calcium level was 0.0102. After exposure to the sun's rays for an hour he showed dyspnea. The calcium level was 0.0100.

It was concluded, then, that the specific influence of the sun's rays is shown in dogs treated with parathyroid extracts.

BIBLIOGRAPHY

Berman, L.: 1923-24. Proc. Soc. Exper. Biol. & Med. (N. Y.), **21**, 465.
Collip, J. B.: 1925. J. Biol. Chem. (N. Y.), **63**, 395-438.
Collip, J. B. and E. P. Clark: 1925. J. Biol. Chem. (N. Y.), **64**, 485-507; ibid, **66**, 133-137.
Collip, J. B., E. P. Clark and J. W. Scott: 1925. J. Biol. Chem. (N. Y.), **63**, 439-460.
Fisher, N. F. and E. Larson: 1925. Am. J. Physiol. (Balt.), **75**, 93-106.
Hanson, A. M.: 1923. Mil. Surgeon (Washington), **52**, 280-284, 1924; **54**, 218-219; ibid, 554-560; 701-718
Hanson, A. M.: 1924-25. Proc. Soc. Exper. Biol. & Med. (N. Y.), **22**, 560-561.
Hjort, A. M., S. C Robinson and F. H. Tendick. 1925. J. Biol. Chem (N. Y.), **65**, 117-128.
Salvesen, H. A.: 1923. J. Biol. Chem. (N. Y.), **56**, 443-456.

A CASE OF DIABETES, REFRACTORY TO INSULIN, WITH HYPERPLASTIC AND ADENOMATOUS ADRENALS

ROBERT A. MOORE

Department of Pathology, The Ohio State University

COLUMBUS, OHIO

There is probably no part of the field of morbid anatomy in which the pathologist is more greatly vexed than in the pathology and correlated physiology of the endocrines. There are available a large number of papers dealing with the physiology, chemistry and pharmacology of the ductless glands, yet we are far from a proper evaluation of the role of these organs in the entire body economy. Again, there are many papers dealing with the pathology of this or that organ in correlation with certain clinical signs or even a disease entity. It is easy to say that destruction of the adrenals is correlated with Addison's disease, yet many obstacles must be hurdled before such a statement is accepted as absolute. What about the 15 per cent of cases of clinical Addison's disease that present no destruction of the adrenals demonstrable at autopsy? Why is an extract of the adrenals of little value in the treatment of the disease? Turning to the thyroid, the pathologist speaks of colloid goitres, parenchymatous goitres and adenomata of the thyroid, while the clinician speaks of thyrotoxicosis, Basedow's disease and other terms which mean little to the pathologists. Each is apparently oblivious of the existence of the other.

Even as complicated as the physiologic pathology of the one endocrine may appear, undoubtedly there are diseases, or at least symptoms resulting from a combined disease of two or more endocrines, a pluriglandular disease. These may be the result of a general systemic disease affecting two endocrine organs, or there may be two independent processes, either of which may influence to advantage or disadvantage the functional derangement of the other.

Despite the known "thin ice" upon which one is treading in correlating pluriglandular pathology with disturbance of func-

tion of the endocrines, I venture to record a possible pluriglandular complex as an explanation of a case recently seen on the autopsy service of Starling-Loving Hospital, at Columbus.

CASE REPORT. M. G., white, female, 34 years of age, was admitted to Starling-Loving Hospital (Case No. 261560) on March 30, 1926, in a state of coma. From subsequent questioning the following history was elicited:

Family History: The mother died at 45 of unknown cause. The whereabouts of the father is unknown. One brother and one sister are living and well. One brother died in infancy.

Past History: During childhood the patient had measles, pertussis, mumps, diphtheria and chicken pox. She suffered a mild attack of influenza in 1918.

Present Illness: In September, 1924 (19 months ago) the patient states that she first noticed fainting spells when she got up in the morning. She also complained of marked polyuria, frequency and nocturia. She was treated on a low carbohydrate diet, until January, 1925, when insulin was started, the dose being 9 units three times a day. In July, 1925, in Washington, D. C., she suffered from what was apparently an attack of diabetic coma, remaining unconscious for 24 hours. The present attack began the same day she entered the hospital.

Physical Examination at the time of admission is essentially uninformative. Her blood sugar was 560 mgm. per 100 cc. Urinalysis showed: sp. g., 1.032; acid; albumin, trace; sugar, 5.8 per cent; no casts; acetone and diacetic acid present. A blood examination showed hemoglobin, 82 per cent; red blood corpuscles, 4,606,000; white blood corpuscles, 12,680; polymorphonuclear leucocytes, 92 per cent. The Wassermann reaction was negative.

Course: Under insulin and glucose therapy the patient made a good recovery from the coma. By the next morning the blood sugar was down to 80 mgm., the urine was acetone-free and the patient fully conscious and feeling fine. Toward noon of this same day she presented symptoms of returning coma and a blood sugar determination revealed 510 mgm. per 100 cc. On insulin and glucose she was brought back to normal, clinically and according to laboratory tests. During the succeeding four days the progress was rather stormy, with alternate periods of semi-coma with a markedly fluctuating blood sugar. While apparently on a rigorous diet and insulin therapy, carefully controlled, on the morning of April 5th the patient again passed into coma. A blood sugar determination at 8:00 a. m. revealed 1075 mgm. glucose per 100 cc. Twenty-five units of insulin apparently had a slight effect. There was a distinct acetone odor to the breath and an abundance of acetone and diacetic acid in the urine. At 10:00 a. m. the blood sugar was 169 mgm. per 100 cc. The patient died at 10:12 a. m., April 5, 1926.

An *autopsy* was performed on April 6, 1926, at the Starling-Loving Hospital, by Dr. Ernest Scott and Robert A. Moore.

The body was that of a rather large, mannish type woman.

The stomach and intestines were somewhat distended with gas. The omentum was normal. The appendix was apparently normal. The peritoneum was smooth. There was no fluid in the peritoneal cavity. The liver was at the costal margin, pale in color and of a slightly yellowish and somewhat mottled appearance. The gall bladder was small and contained no calculi. The spleen was normal in size. In the thoracic cavity there were adhesions over the upper lobe on the right side. There was no increased fluid in either pleura. The left lung was free, and there were areas of consolidation. The pericardial sac was normal.

Organs of the Abdominal Cavity: The pancreas was rather thin, flat and somewhat flabby in its structure. The glandular tissue was somewhat reduced in amount. No areas of fibrosis or other focal or diffuse pathologic changes were noted. The spleen was normal in size and color. On section, the pulp substance was solid and paler than normal. The left adrenal gland was thickened with apparently very great increase in cortical substance. This increased substance was of yellowish color. On section, the adrenal gland showed a diffuse adenomatous growth measuring 1 by 1 cm. in the cortex. The left kidney was of usual size; the markings were very distinctly retained. The cortex was of usual thickness, measuring 6 mm. The right kidney was silimar to the left. The adrenal gland on the right side was also large and contained a distinct adenomatous nodule measuring 1½ by 1 cm. The uterus contained an early menstrual flow in the endometrium; otherwise it was normal. The right ovary was cystic. The urinary bladder showed a purulent cystitis, but was otherwise normal. The liver was slightly enlarged; the cut surface was pale, rather yellowish and mottled.

Organs of Thoracic Cavity: Careful examination of the lungs, heart and mediastinum failed to reveal any active pathologic change. There were a few scars at the right apex and a calcified nodule in the center of the upper lobe. The thyroid was not unusual.

The Head: Examination of the meninges and brain showed no abnormalities. The pituitary gland was apparently normal.

Microscopic Examination: Thorough microscopic examination of the pancreas demonstrated that the majority of the islands of Langerhans were structurally normal. A few islands showed atrophy, hyaline degeneration and fibrosis. There was no other associated abnormality in the acini, interstitial tissue, ducts or blood vessels of the pancreas. The adenomatous nodules in the adrenals presented the typical appearance of adrenal cortex, with nothing to distinguish them microscopically as tumors. The remainder of the organs presented microscopically no abnormalities.

Anatomic Diagnosis: Hyaline degeneration and fibrosis of the islands of Langerhans, cortical adenomata of the adrenals, and purulent cystitis.

SUMMARY

The case is reported of a woman of 34 who died in diabetic

coma despite very large doses of insulin. The blood sugar shortly before death was 769 mgm. per 100 cc. At autopsy the pancreas was found to be normal except for atrophy of a small proportion of the islands of Langerhans and slight reduction in the amount of glandular tissue. The only other endocrine abnormality found was an adenomatous and hyperplastic pair of adrenal glands.

I am indebted to Dr. G. I. Nelson for the clinical history of this case.

OVARIAN AND PLACENTAL HORMONE EFFECTS IN NORMAL, IMMATURE ALBINO RATS

GEORGE T. GOLDING AND F. T. RAMIREZ

Department of Anatomy, University of Missouri

COLUMBIA

INTRODUCTION

This experiment was planned to study the effects of active extracts of the ovary and placenta in normal, immature male and female albino rats.

Much has been written in recent years on the effects of injections of these hormones into the rabbit, mouse and rat, both in mature and immature animals. Little attention, however, seems to have been paid to recovery after injections are discontinued. There also remains some disagreement as to antimasculine effects of these hormones, as will be brought out in the discussion of the literature. Consequently the present paper seeks to establish definite hormone effects and then to follow through the period of recovery in several animals.

LITERATURE

In a recent paper Allen and Doisy (1927) presented an extensive review of the experimental work thus far accomplished on ovarian and placental hormones. The work to date on this subject has demonstrated that there is a casual relationship between the internal secretion of the ovaries and the oestrous cycle in female animals and the menstrual cycle in the primates. Injections of ovarian follicular hormone into spayed animals, normal animals during inactive periods, and pregnant and lactating animals were found to produce oestrous changes with the characteristic reactions of the genital system. Later it was discovered that placental extracts produce the same results as the ovarian follicular hormone when injected into female animals.

The effects of ovarian and placental hormones on the female genital organs seem to be well established, but the effects on the testes and male genital organs are not so well agreed upon.

Herman and Stein (1920) reported that injections of extracts of corpus luteum into young male rats and rabbits delayed the attainment of sexual maturity and that prolonged injections of larger quantities of the corpus luteum extract in adult rats and rabbits led to degenerative changes in the testes. Fellner (1921) also found degeneration of the testes produced by injections of lipoid extracts of placenta or of corpus luteum. Bugbee and Simond (1926) reported the absence of antimasculine effects from injections of follicular hormone, while Laqueur (1926), with a highly purified extract, menformon, found definite antimasculine effects. Therefore, the question as to the effect of this hormone on the male genital organs is still to be finally decided.

PROCEDURE

In this experiment normal young albino rats of two separate litters were used. The first litter consisted of three females and six males. Of these one male and one female were used as controls and the others used as test animals. In the second litter there were four females and seven males. Of these one female and two males were used as controls and the others as test animals. This made a total of five controls and fifteen test animals. Injections were begun simultaneously in all the animals when the first litter was eighteen days old and the second litter twelve days old. Follicular hormone (Squibb) was injected into the test animals and an equal amount of Ringer's solution into the controls. Injections were made twice daily, at approximately eight o'clock in the morning and five o'clock in the afternoon. The younger rats were started with 0.2 cc. injections of extract which contained five rat units per cc. The potency of this extract was standardized by tests in spayed mature female rats. The older rats were given 0.25 cc. of the same extract. Therefore, the animals were receiving respectively two and two and one-half rat units each day. This procedure was continued for eight days. Weights of the rats were recorded daily at five o'clock and observations noted as to the condition of the vagina and position of the testes. On the ninth day after the beginning of injections and each day following, injections were increased in amount so that there was an addition of 0.25 rat units each day.

After fourteen days, due to a shortage of Squibb's extract, "Estrogen" (Parke, Davis Co.§), diluted to five rat units per cc., was substituted. The same daily increase of 0.25 rat units was continued and weights and observations recorded. After twenty-two days of continual injections the two male controls of the younger animals were sacrificed together with three injected males of the same litter. These animals had received a total of 74 rat units in twenty-two days, as shown in the following tables.

TABLE I
Males

Rat	Treatment	No. Days Injected	No. Rat Units Injected
MN_1Ra	Control	Ringer's	0
MNNa*	Injected	35	214
MNRa	Injected	24	124
MSBa	Injected	24	124
MNLa	Injected	24	124
M_2Na*	Injected	24	124
MNNB	Control	Ringer's	0
MSREB	Control	Ringer's	0
MNRB	Injected	20	74
MNLAB	Injected	20	74
MNLB*	Injected	36	192
M_2NB	Injected	25	102

*All animals were killed immediately after the last injection of extracts, with the exception of animals MNNa, M_2Na, MNLB, which were observed for 14, 11, 13, and 11 days, respectively, during the period of recovery from effects of the hormone.

TABLE II

Rat	Treatment	Body Weights		No. of Days Injected	No. R. U. Injected	Vagina Opened	Wt. of Thymus Grams
		At Start Grams	At Death Grams				
FN_1La	Control	21.0	78.5	Ringer's	0	Closed	.223
FNNa*	Injected	18.0	90.0	24	124	After 9 days	.147
FNRa	Injected	18.0	71.1	24	124	After 9 days	.163
FNNb	Control	15.0	62.3	Ringer's	0	Closed	.203
FNRb	Injected	13.5	64.5	24	101	After 13 days	.180
FSLEb*	Injected	10.0	58.8	25	102	No record	.161
FSBHb	Injected	12.0	69.2	36	192	After 14 days	.171

*All animals were killed after the last injection of extract, with the exception of animals FNNa and FSLEb, which were observed for 12 days during the period of return to normal.

§Estrogen, Parke, Davis & Company's preparation. The writer wishes to acknowledge the assistance of both E. R. Squibb & Sons and Parke, Davis & Co. for considerable supplies of active extracts.

Weights were taken of the entire body, genital organs and thymus. These tissues were then fixed in Bouin's fluid together with the other endocrine glands and prepared for histological study. The following week a number of the other animals were sacrificed. All this time the increase in amounts of injections of 0.25 rat units per day was continued in the other animals. These animals had received 124 rat units in twenty-four days, as shown in the above tables. This left only four of the younger rats, of which two were males and two females, and three of the older animals, of which one was a female and two were males, all of which had been continually injected. From this point on there were no increases in the amount of injections because of the excessive doses the animals were already getting. Of the younger four, one male and one female were kept alive without further injections while injections into the other two were continued. These animals received six rat units each day without any increases. This same amount was also injected into one of the older males while injections were discontinued in the other two animals. After 36 days all but one male of each litter which had been continuously injected were sacrificed. These two males had by this time had 192 and 214 rat units of hormone respectively. These animals were carefully observed in the following days for signs of the descent of the testes into the scrotum.

OBSERVATIONS AND DISCUSSION

The injections caused no retardation of body growth of any of the animals as was reported by Bugbee and Simond (1926). All animals increased in weight, averaging about twenty-eight grams per two weeks for the older animals, and twenty-five grams for the younger rats. The males gained more weight than the females in both the injected and control animals. In the daily record there was an average increase of approximately two grams per day for all the animals.

When the animals were sacrificed it was invariably found that the thymus of the injected animal was smaller than that of the control (Figs. 1 and 2). The thymus of the control male of the larger litter weighed 0.231 grams as compared with 0.223 grams for that of the female control. The average weight of the thymus of the injected males was 0.182 grams as compared with

0.155 grams for the injected females. These were all under the same environmental conditions and killed within one day of each other. In the younger animals the thymus of the control male weighed 0.214 grams as compared with 0.203 grams for that of the female control. The average weight of the thymus of the injected animals was 0.170 grams for the females and 0.128 grams for the males. These weights are for those animals which were injected for twenty-four days. In the female which was injected for thirty-six days the thymus weighed 0.171 grams or approximately the same as the others. But in the male which was injected for 25 days after which injections were discontinued for eleven days, the thymus weighed 0.303 grams. This

FIGURES 1 AND 2

would tend to show that the injection of the hormone inhibits the growth of the thymus, but with the subsequent discontinuation of the injections, recovery seems to occur quite readily and quickly. This point should be checked in a greater number of animals.

The first manifestation of hormonal effects in the treated female animals was the opening of the vagina which occurred in the older animals after nine days of injections and in the

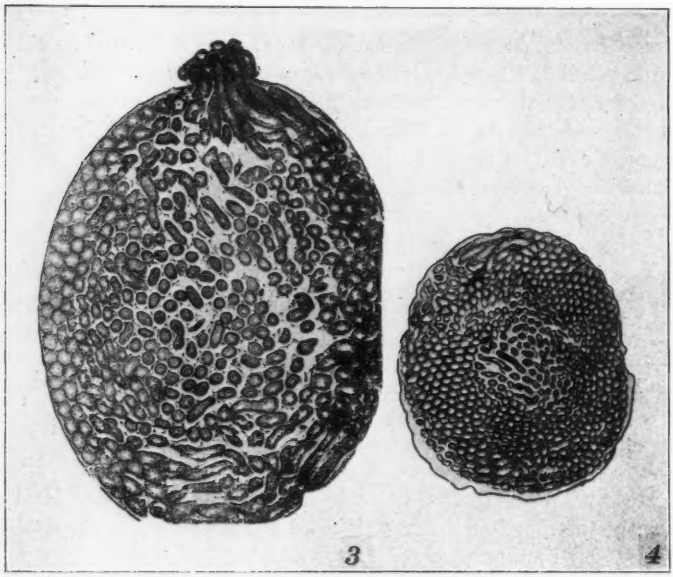
younger rats after 13 and 14 days. The vagina of the control animals at this period remained closed. Vaginal smears of the injected animals showed cornified cells which were sloughed off or desquamated from the lining mucosa of the vaginal wall. But after discontinuing the injections for observations on the after effects the daily smears showed a normal four-day oestrous rhythm for the following two weeks after which smears were discontinued.

Grossly there were no conspicuous changes observed in the ovaries of the treated animals except that they appeared to be smaller than the ovaries of the controls. But histologically the ovaries of all the animals were similar. They were characterized by a great number of developing follicles of various sizes and an abundance of interstitial tissue. The larger follicles appeared to be undergoing atresia. There were no corpora lutea in the ovaries of either of the injected or control animals, consequently ovulation had not occurred.

Histological preparations of the vagina and uterus showed a marked hyperplasia of these organs in the injected animals as previously described by Allen and Doisy, '24. It is evident from these results that the injection of ovarian and placental hormone into immature female rats induces growth of the vagina and uterus but in large doses over long intervals does not stimulate the growth of follicles in the ovaries.

In the males the size and weight of the genital organs of the control animals was twice and three times that of the injected rats (Figs. 3 and 4). The genital organs of the control animals of the older litter weighed 1.369 grams while those of the injected animals ranged from 0.401 to 0.672 grams. In the younger animals the genital organs of the control weighed 1.112 grams as compared with 0.203 and 0.163 grams for the injected animals. One male, which had been injected for 25 days, after which injections were stopped for eleven days, contained genital organs weighing 0.673 grams. The weights and sizes of the testes corresponded comparatively to that of the other genital organs. More noticeable than this condition, however, was that of the position of the testes in the various animals. In all animals which had had continued injections the testes remained in the abdomen, while the testes of the control animals descended into the scrotum. In the larger animals the weight of

the testes of the control averaged 0.974 grams, and measured 9x9x14.5 mm. and was in the scrotum when killed; while the weights of the testes of the injected animals ranged from 0.246 to 0.436 grams and measured from 4.5x5x8 to 6.5x7x10 mm. and were all located in the abdomen. In the animals in which injections were discontinued for eleven days the weight of the testes averaged 0.369 grams and measured 7x7x10 mm., but had just concluded the descent into the scrotum. With the younger



FIGURES 3 AND 4

animals approximately the same results were obtained and the time for the descent after discontinuing injections was about eleven days. Those animals in which injections were continued for 36 days and then discontinued, required 13 and 14 days for the complete descent of the testes into the scrotum.

That a block in the growth of the testes was produced was further shown histologically. There were no spermatozoa nor spermatids in the testes of injected animals (Fig. 4), while many spermatids and a few spermatozoa were found in the testes of

the control animals (Fig. 3). In the controls there were also numerous thick mitotic layers in the tubules and much interstitial tissue while in the injected animals there were very few mitotic figures and no insterstitial tissue. In these animals where injections were discontinued for eleven days few spermatids were found in the tubules.

TABLE III

Males

Rat	Treatment	Body Wts.		Wt. of Thymus Gm.	Wt. of Genitals Gm.	Wt. of Testes Gm.	Size of Testes MM.	Position of Testes
		At Start	At Death					
MN_1Ra	Control	21.5	99.8	.231	1.369	.974	9x9x14.5	In scrotum
MNNa	Injected	20.0	83. After 4 weeks					11/23 stop injections 11/23 in abdomen 11/30 in abdomen 12/7 in scrotum
MNLa	Injected	21.0	82.1	.173	.672	.436	6.5x7x10	In abdomen
MNRa	Injected	19.5	80.0	.192	.483	.261	5.5x6x 8.5	In abdomen
MSBa	Injected	19.5	76.3	.183	.401	.246	4.5x5x 8	In abdomen
M_2Na*	Injected	20.0	112.5	.219	.836	.369	7x7x10	In scrotum
MNNb	Control	14.5	62.7	.212	1.112	.610	7x8x12	In scrotum
MSREb	Control	15.0	61.6	.214	1.099	.436	6.5x7x12	In scrotum
MNRb	Injected	12.5	53.7	.122	.203	.061	3.5x3x 5	In abdomen
MNLAb	Injected	14.5	51.1	.134	.163	.064	3x3x 6	In abdomen
MNLb	Injected	15.5	After 4 weeks 70.0					11/24 stop injections 11/24 in abdomen 12/7 in scrotum
M_2NB*	Injected	12.0	93.3	.303	.673	.295	6.5x7x10	In scrotum

*All animals were killed after the last injection of extract, with the exception of animals M_2Na and M_2NB, which were observed for 11 days before sacrificing. MNNa and MNLb were not killed. These animals were also kept under observation after discontinuing injections.

SUMMARY

This experiment consisted of injecting water-soluble preparations of hormone into male and female rats from two litters beginning at ages of 12 and 18 days. Injections were made twice a day starting with 2 rat units and increasing the dose daily for from 20 to 36 days. The total dose ranged from 74 to 214 rat units.

Some of the injected animals were killed for histological comparison with controls; others were observed for after effects.

In the males there was an inhibition of growth of the genital organs and the testes remained in the abdomen. This was obvious in the living and was further checked by weights, measurements and histological preparations. The genital organs

of the controls were much larger, and the testes descended into the scrotum during the experiment. Injected males observed after discontinuing injections required from 10 to 15 days for descent of the testes. After 20 days these testes appeared normal.

In injected females the vagina opened, while in the controls it remained closed. Vaginal smears during injections showed continuous oestrus; upon discontinuing injections, smears showed normal cycles. Histological sections of vagina and uterus showed same evidences of oestrous changes. There were no corpora lutea in the ovaries of either control or injected animals.

The weights of the thymus glands of injected rats were about half those of the controls.

The writers wish to acknowledge their indebtedness for the suggestions and assistance of Dr. Edgar Allen during the course of this work.

BIBLIOGRAPHY

Allen, E. and E. A. Doisy. 1927. Ovarian and placental hormones. Physiol. Reviews, **7**: 600.

Allen, E. and E. A. Doisy. 1924. The induction of a sexually mature condition in immature females by injection of the ovarian follicular hormone. Am. J. Physiol. **69**: 577-588.

Bugbee, E. P. and A. E. Simond. 1926. Effects of injections of ovarian follicular hormone on body growth and sexual development of male and female rats. This Journal, **10**: 360-369.

Bugbee, E. P. and A. E. Simond. 1926. The influence of testes on metabolism. Am. J. Physiol. **75**: 542-547.

Fellner, O. O. 1921. Arch. f. d. ges. Physiol. **189**: 199.

Herrman, E. and M. Stein. 1919. Zentralbl. f. Gynäk. **42**: 425.

Abstract Department

The comparative sensitiveness to epinephrin of blood pressure and intestinal motility in man. Dragstedt, C. A. and J. W. Huffman. Am. J. Physiol. **85**: 363. 1928.

As previously reported, pressor effects in the unanesthetized dog may be obtained on sustained injection of epinephrin in the absence of intestinal inhibition. Danielopolu, Simici and Dimitri reported that in man 1 cc. of 1 to 300,000 adrenalin exaggerated the peristaltic contractions of the small intestine, but that 1 cc. of 1 to 100,000 produced an inhibition. They did not report simultaneous observations on blood pressure. Csepai reported that with intravenous injections in man, the average patient gave a rise in pressure of 20 to 30 cm. of water with 1 cc. of 1 to 100,000 epinephrin. No simultaneous observations of intestinal motility were reported. We have made simultaneous observations of blood pressure and intestinal motility in man after injection of epinephrin, and have seen blood pressure rises of 15 mm. in the absence of any effect on intestinal motility.—Authors' Abst.

Vasomotor responses to perfused adrenalin in the unanesthetized dog. Durant, R. R. and J. H. McNinch. Am. J. Physiol. **85**: 364. 1928.

The spleens of two young female dogs were externalized by the method described by Barcroft and Stephens. After a short recovery period, during which the incisions had healed completely, the volume changes of the spleens were recorded by means of an oncometer strapped to the abdominal wall. Blood pressure was recorded separately and also simultaneously with the spleen volume, by the direct method. The cannula was inserted in the femoral artery under local novocain anesthesia. Intravenous injections of minimal doses of adrenalin (Parke, Davis & Co.) were found to produce only rises in blood pressure and constriction of the spleen. These observations confirm those of Dragstedt and lend support to the "emergency" theory of suprarenal function.—Authors' Abst.

The accumulation of sulphur in the skin after adrenalectomy (L'accumulation du soufre dans la peau apres surrenalectomie). Loeper, M., J. Decourt and A. Lesure. Compt. rend. Soc. de biol. **98**: 1098-1099. 1928.

In three dogs there was a marked increase of sulphur in the skin following the removal of one adrenal.—J. C. D.

Muscular fatigue in decapsulated rabbits (La fatigue musculaire chez les Lapins privés de capsules surrénales). de Mira, F. and J. Fontes. Compt. rend. Soc. de biol. **98**; 987-989. 1928.

Action of adrenin on the activity of fatigued muscle in decapsulated rabbits (Action de l'adrénaline sur la contractilité du muscle fatigué chez le Lapin privé de capsules surrénales). de Mira, F. and J. Fontes, Compt. rend. Soc. de biol. **98**: 1011-1013. 1928.

Further observations on the relation between the adrenals and muscular action (Nouvelles recherches sur les capsules surrénales dans leurs rapports avec la fonction musculaire). de Mira, F. and J. Fontes. Compt. rend. Soc. de biol. **98**; 1013-1015. 1928.

Flexor muscles of the foot were used in anaesthetized animals and their activity under electrical stimulation recorded on an ergograph. Compared with controls, the decapsulated animals showed three types of reaction according to whether the adrenal insufficiency was slight, marked, or very severe. (a) The muscle became rapidly exhausted, but recovered its initial power after a short rest. (b) The rapid exhaustion of the muscle as in (a) was followed by failure to recover after rest. (c) The initial reaction was very weak and there was no recovery after rest. Injections of adrenin extract, of whole gland and extract of cortex, failed to relieve the fatigue, and in most cases actually hastened it.—J. C. D.

Studies on adrenal insufficiency. VI. The influence of "heat" on the survival period of dogs after adrenalectomy. Rogoff, J. M. and G. N. Stewart, Am. J. Physiol. **86**: 20-24. 1928.

"Heat" in four dogs was associated with a marked lengthening of the survival period and the period of good health after removal of the adrenals. One lived into the 22nd day after excision of the second adrenal; one lived 32 days; one lived into the 37th day, and one into the 65th day. Nothing like these survival periods was seen in about 150 control dogs.—R. G. H.

Studies on adrenal insufficiency. VII. Further blood studies (cholesterol and calcium) in control adrenalectomized dogs. Rogoff, J. M. and G. N. Stewart, Am. J. Physiol. **86**: 25-31. 1928.

The calcium content of the blood serum of 12 adrenalectomized dogs was generally found increased at the time of or sometimes a little preceding the development of the serious symptoms, especially anorexia, which terminate the period of good health. No significant change in blood cholesterol was found.—R. G. H.

The effect of adrenaline on an isolated heart after thyroidectomy (Die Reaktion des isolatierten Herzens eines thyreoidektomierten

Tieres auf Adrenalin). Schermann, S. J., Arch. f. exp. Path. u. Pharmakol. **126**: 10. 1927. Abst., Physiol. Absts. **13**: 181,

The threshold dose of adrenaline in the isolated heart of the rabbit was determined. In the case of 6 rabbits whose thyroids had been removed 15 to 70 days before, it was 20 to 50 times higher than in the case of 6 rabbits who had undergone a similar operative technique without actually losing their thyroids.

The effect of thyroidectomy and of forcing fluid on the susceptibility to toxins in suprarenalectomized rats. Wyman, L. C., Am. J. Physiol. **85**: 413-414. 1928.

It has recently been shown (Corey, Zwemer, 1927,) that forcing fluids or thyroidectomy (thereby decreasing elimination of water) prolongs the life of suprarenalectomized cats. Dehydration is one of the symptoms of suprarenal insufficiency in rats. In a series of 30 rats which had been completely thyroidectomized one or two weeks previous to double suprarenalectomy, 40 per cent died of acute or subacute suprarenal insufficiency within 21 days after the latter operation. These animals showed the usual symptoms of acute or subacute insufficiency and at death the usual number showed such findings as diarrhea, bloody nose and eyes, and congested stomach and intestines. Of those which survived, 10 had gained weight in the period between thyroidectomy and suprarenalectomy, but during the three weeks following suprarenalectomy 10 lost weight and only 3 gained. Of these latter one was found at autopsy to have gross accessory cortical tissue. In a series of 137 control rats which had been doubly suprarenalectomized without previous treatment, 42.3 per cent died of acute or subacute suprarenal insufficiency. The lethal dose of diphtheria toxin, administered intraperitoneally, averaged 2.75 M.L.D. per gram of body weight both for the thyroidectomized-suprarenalectomized rats and for the suprarenalectomized rats. The lethal dose for normal or blank operated rats averaged 6 M.L.D. per gram of body weight. Both sets of suprarentalectomized rats were, therefore, 2.18 times as susceptible to diphtheria toxin as the controls. Both thyroidectomized-suprarenalectomized rats and suprarenalectomized rats were killed quite regularly by doses of 7 mgm. of histamine acid phosphate per hundred grams of body weight. All which survived such doses were shown at autopsy to have gross accessory suprarenal tissue. Normal or blank operated rats survived doses of histamine acid phosphate up to 100 mgm. per hundred grams of body weight. Fluid was administered to rats by means of daily intraperitoneal injections of 10 cc. of a 5 per cent solution of glucose during a period of three to five days at two to four weeks after double suprarenalectomy. Following this treatment, the rats were killed by doses of from 5 to 10 mgm. of histamine acid phosphate per hundred grams of body weight. Preliminary experiments indi-

cate that similar administration of glucose solution does not decrease the heightened susceptibility of suprarenalectomized rats to diphtheria toxin. It appears that thyroidectomy does not decrease the acute and subacute mortality percentage after suprarenalectomy. Also, thyroidectomy or forcing fluids does not decrease the heightened susceptibility of suprarenalectomized rats to the toxins investigated. This suggests that impaired ability to flush toxins out of the body, due to dehydration, is not an important part of the picture of increased susceptibility.—Author's Abst.

The effect of suprarenal insufficiency on the oestrous cycle in the albino rat. Wyman, L. C., Am. J. Physiol. **85**: 414-415. 1928.

Of a series of 14 doubly suprarenalectomized female rats which were exposed to males two weeks after operation, 7 became pregnant and gave birth to normal litters. Of the 7 that did not become pregnant, 4 died of subacute suprarenal insufficiency within two weeks after exposure to the males. The other 3 were left with the males for two or three months and were then killed. At autopsy no gross accessory suprarenal tissue was found. In 6 of the group that had litters gross accessory cortical tissue was found at autopsy. These results suggest that ability to reproduce after double suprarenalectomy is correlated with the degree of suprarenal insufficiency remaining after operation. In a series of 17 female rats, daily vaginal smears were studied, both before and after double suprarenalectomy. Fourteen of this group died of acute or subacute suprarenal insufficiency within 27 days after operation. With one exception these rats showed no oestrous changes in the vaginal smears from the time of operation until death. In the one case the smears were characteristic of oestrous for the 7 days preceding death. In the 3 rats that survived longer, there were dioestrous pauses after operation lasting from 21 to 36 days, following which oestrous changes appeared at irregular intervals and were separated by much prolonged dioestrous pauses. These rats were exposed to males and 2 became pregnant. One of these gave birth to a normal litter and at autopsy was found to have a large accessory suprarenal mass; the other died of chronic suprarenal insufficiency on the seventeenth day of pregnancy. In order to control for operative trauma, the vaginal smears were studied as before in a series of 12 rats in which one suprarenal gland was removed and the other gland was exposed and handled. This procedure did not disturb the regular occurrence of vaginal oestrous changes. The remaining suprarenal gland was later removed. Following this, 5 rats died of acute or subacute suprarenal insufficiency. In 2 of these there was no change in the occurrence of oestrous changes other than a slight prolongation of the oestrous period. The other 3 had prolonged dioestrous pauses. Of the 7 that survived, 3 showed no significant changes in the occurrence of vaginal oestrous changes and 4 had occasional

much prolonged dioestrous pauses. It appears that in suprarenal insufficiency in the albino rat there may be partial or total inhibition of vaginal oestrous changes, presumably due to suppression of ovulation. It is not known whether there is a direct relationship between the functioning of the suprarenal gland and the production of ovarian hormones or an indirect relationship through the mediation of other factors. The irregularity of the effect of suprarenalectomy suggests the latter.—Author's Abst.

Endocrine and biochemical studies in schizophrenia. Bowman, K. M., J. Ner. & Ment. Dis. **65**: 465-483; 585-604. 1927.

A study of twenty-four cases of schizophrenia was made, using tests which would have a special relationship to endocrine function. An abnormally low level of basal metabolism was found in half of the cases, with a tendency towards low or minus readings in nearly all the other cases. Nearly one-half of the cases showed an abnormal blood sugar curve, all but one being of the "sustained" type. Over one-third showed a positive galactose tolerance test. X-ray examinations and gastric analyses showed a definite functional disorder of the gastro-intestinal tract in about half of the cases and questionable functional disorders in all but two of the other cases. X-ray examinations further revealed infected teeth in 40 per cent of the cases, with questionable infection in 10 per cent more. X-ray examinations also revealed "dropped" hearts in 30 per cent of the cases, questionable pulmonary tuberculosis in 13 per cent and healed pulmonary tuberculosis in 4 per cent (one case). The findings are not consistent with the constant presence of any definite endocrine disorder, and do not suggest that a simple glandular dysfunction of a constant type is an etiological factor in schizophrenia. Rather they suggest that many functional disorders, closely linked up with the endocrine system, are frequently found and that schizophrenia is not a specific endocrine disease, but may arise on a number of different bases. The one constant finding appears to be that a metabolic disorder of varying degree is nearly always present as manifested in functional gastro-intestinal disorders and a tendency toward low basal metabolism which are present in the majority of cases.—Author's Abst.

Histological changes in the female reproductive organs under the influence of the hormone of the corpus luteum (Modifications histologiques du tractus genital femelle sous l'action de l'hormone du corpus jaune). Gley, P., Compt. rend. Soc. de biol. **98**: 834-837. 1928.

In the female rat, daily injections of corpus luteum extract inhibit the growth of Graafian follicles so that only undeveloped or small sized ones are found. The uterus and the vagina resembles those of a spayed animal. Evidently the normal oestrous cycle is

dependent on the follicular hormone, which brings about oestrous, and the hormone of the corpus luteum, which causes regressive changes. This regression goes on until the corpus luteum degenerates and the follicular hormone again begins to act.—J. C. D.

Cytological studies on the human corpus luteum (Recherches cytologiques sur le corps jaune de la Femme). The ovarian and uterine cycles in the human (Cycle ovarien et cycle utérin chez la Femme). Horrenberger, R., Compt. rend. Soc. de biol. **98**: 849-851. 1928.

The cells of the corpus luteum show an active phase characterized by "chondriocontes" and mitochondria and a phase of involution in which these disappear and fatty degeneration takes place. In the thecal cells similar changes occur, but they precede those in the lutein cells. The uterine cycle ends with menstruation and that of the ovary with the degeneration of the corpus luteum. These cycles are occurring simultaneously and the ovarian cycle is influencing the uterine. Ovulation occurs at a variable time in the intermenstrual period and is to a certain extent independent of the formation of the corpus luteum.—J. C. D.

Effect of lutein injections on oestrous cycle of the guinea pig. Macht, D. I., A. Stickel and D. Seckinger. Am. J. Physiol. **85**: 389-390. 1928.

The oestrous cycle in guinea pigs was studied over a period of several years by the vaginal smear method of Papanicolaou, Stockard and others. Water-solubie extracts of corpus luteum were obtained by two methods. According to one method, freshly desiccated corpus luteum was extracted with petroleum ether, then with pure ether and again with pure ethyl acetate, evaporated to dryness, the residue taken up in aqueous bicarbonate solution and finally neutralized with hydrochloric acid. In the second method, the corpus luteum was extracted with weak alcohol deproteinized with subacetate of lead, freed from excess of lead with sulfuric acid, evaporated on the water bath to remove alcohol, and again neutralized. Corpus luteum was obtained in the fresh state from cows in some experiments and from the pig in others. Control experiments were made with injections of follicin and extracts of ovarian residue, placenta and various glands. Daily injections intraperitoneally of 1 cc. of the aqueous lutein solution (equivalent to 5 mgm. of the residue) produced a distinct inhibition of the oestrous cycle, which was suppressed in some animals for as long as seventy or more days. When the injections were discontinued, the normal cycle was quickly re-established. In the present investigation only perfectly healthy animals were used, as it was found that when the animals were diseased the oestrous cycle became very irregular.

—Authors' Abst.

Experiments with follicular and placental extracts. Oslund, R. M., Am. J. Physiol. **85**: 398. 1928.

Feeding of follicular or placental extracts is ineffective. Young female rats were given five unit doses of Estrogen (Parke, Davis & Co.) per day over a period of five days. No oestral changes were found by the vaginal smear method. Estrogen applied to the vagina in minimal doses was followed by positive oestral changes. Though follicular and placental extracts when injected subcutaneously or intraperitoneally, or when applied to the vagina, invoke positive oestral changes, as determined by the vaginal smear method, they do not bring about receptiveness on the part of the female for the male. In three series of spayed rats (18 rats) and in four series of unoperated rats (30 rats), all of which gave positive oestral smears over a period of from one to ten days, all females vigorously fought off males four or five times daily. In another series, five rats were spayed and autotransplants made of their ovaries. One month later they were kept in oestrus over a period of nine days. One rat of this series received several males on the seventh day. All others vigorously fought off males four or five times daily. That the failure to obtain positive copulatory results did not lie in the extract was determined by injecting fresh follicular fluid obtained from hog ovaries. The same results were obtained.

—Author's Abst.

Importance of the site of attachments of testicular transplants (L'importanza della sede per l'attecchimento dei trapianti testicolari). Trichera, C., Policlinico (sez. chir.), **33**: 484-496. 1926. Abst., Biol. Absts. **1**: 1066.

Transplants in the dog were made by the technique of Voronoff not only on the vaginal serosa, but on the parietal peritoneum, parietal pleura, subcutaneous, intramuscular, perirenal fat, bone marrow, and in the parenchyma of spleen and of testicle. After an equal lapse of time (1 month) histological examination of the transplants have uniformly shown a pure involution of the epithelial cells with their more or less rapid resorption until complete disappearance; and a corresponding proliferation of the connective tissue of the host organ, which finally penetrated the intertubular spaces. An increased libido resulted, whatever the site of the transplant. If the hormone function of the testicle belongs to its epithelial elements, as urged by some, these results are thought definitely to contradict Voronoff, who postulates a specificity of site of transplant; for, it is found, that transplants from all sites, including the vaginal, gave homologous results.

What should one think of the "heart hormones"? (Que doit-on penser des "hormones cardiaques"?). Mouzon, J., Presse med. **37**: 582. 1928.

Mouzon reviews the literature and gives an extensive bibliography on the subject. He concludes that it would be premature, at present, to draw conclusions concerning the usage of myocardial extracts in cardiological therapeutics, or even concerning any of the products precociously misnamed "heart hormones." However, in spite of the controversies which continue to render the question difficult, the experimental facts now permit a careful study of the hormone factors which act on the mechanism of heart contractions. One may follow with interest the work, which will, some day, give a true physiological medication of the myocardium.—R. G. H.

Quantitative estimation of posterior pituitary lobe secretion in cerebrospinal fluid of epileptics (Der Gehalt des Epileptikerliquors an Hypophysenhinterlappensekret). Altenberger, H. and F. Stern. Ztschr, f. d. ges. Neurol. u. Psychiat., **112**: 691-710. 1928.

The cerebrospinal fluid of 80 non-epileptics examined by the oxytocic method showed pituitrin-like substance in 71 instances, with an average strength in lumbar fluid of 580 μmgm. (micromilligrams) (64 specimens: 10-1,000 μmgm.), and in ventricular fluid 870 μmgm. (7 specimens: 50-1,000 μmgm.). In 39 of 80 epileptics the substance was found to average 520 μmgm. (160-1,400 μmgm.) in lumbar fluid, while in 40 lumbar, suboccipital, or ventricular fluid was found inactive. The authors believe that pituitary hypofunction must be added to the list of exciting factors for epileptic seizures.

—A. J. McLean.

Further observations on the diuretic substance of experimental diabetes insipidus. Bourquin, H., Am. J. Physiol. **85**: 354-355. 1928.

The following additional properties of the diuretic substance present in the blood and in extracts of the mammillary bodies and adjacent tissue of the brains of dogs suffering from experimental diabetes insipidus have been demonstrated. It is precipitated from solutions made weakly alkaline with barium hydroxide; is insoluble in ether, acetone, and ethyl alcohol; is completely destroyed by ashing; and is labile in solutions strongly alkaline even at room temperature, and in neutral extracts of the mammillary bodies allowed to stand at room temperature. The freshly secreted urine of dogs suffering from experimental diabetes insipidus, evaporated to a small volume, treated with ten or more volumes of cold ethyl alcohol to remove the toxic substances, redissolved and filtered to remove the proteins, causes a prolonged diuresis accompanied by pronounced thirst when injected intravenously into normal dogs. Control injections of urine secreted over the same period of hours by a normal dog of the same weight, in which diuresis has been induced by giving water per orum, causes a comparatively slight and very transitory diuresis unaccompanied by thirst. This substance

is presumably identical with the diuretic substance present in extracts of the mammillary bodies and in the blood of these dogs, for it possesses the same properties. A diuretic substance also having these same properties has been demonstrated in extracts from the mammillary bodies and adjacent tissue taken from the brains of freshly slaughtered hogs, sheep, and cattle, but not in extracts of similar quantities of tissue selected at random from other portions of the same brains. The substance is present in comparatively small amount, for the extract from five to six hundred hog brains produces about the same degree of diuresis as that which is caused by the extract from the mammillary bodies of the brains of three to five diabetic dogs.—Author's Abst.

The effect of daily transplantation of the anterior lobe on the course of pregnancy in the rat and mouse. Engle, E. T. and Camille Mermod. Am. J. Physiol. **85**: 518-526. 1928.

Daily homeotransplants of fresh anterior lobe of pituitary were given to 45 mice and 25 rats. If given in the first third of pregnancy, implantation or early resorption of the ova occurred. If treatment is begun during the middle third of the period of gestation, resorption or expulsion of the fetus took place. Pregnancy was interrupted less often when treatment was begun in the latter third of pregnancy. Many normal litters were born at term in this series. It is thought that abortion or resorption would occur in every case were a sufficiently large amount of hormone introduced. The gonad-stimulating hormone of the anterior pituitary, introduced by the fresh transplant method, resulted in the production of a large number of ovarian follicles. The ovarian hormone thus produced caused a proliferation of the uterine mucosa, bringing about a condition similar to that in normal oestrus. Pregnancy appears to be incompatible with these conditions. Many tubal ova were found in those cases which were studied microscopically after abortion had occurred. Ovulation did not occur during pregnancy, but followed its termination.—R. G. H.

Contribution to the study of the function of the anterior lobe of the hypophysis (Contribution a l'étude du fonctionnement du lobe antériur de l'hypophyse). Grueter, F., Compt. rend. Soc. de biol. **98**: 1215-1217. 1928.

Aqueous extracts of the anterior lobe were injected into immature female rabbits. In the former, there was a remarkable development in the number of ripening follicles and corpora lutea accompanied by marked congestion of the genital tract. In the latter, injection resulted in suspension of oestrous, development of corpora lutea in large numbers, and appearance of milk in the mammary glands.—J. C. D.

Physiology and pathology of the pituitary (Beitrage zur Physiologie und Pathologie der Hypophyse). Poos, F., Klin. Wchnschr. **6**: 1884. 1927. Abst., Physiol. Absts. **13**: 183.

A summary is given of a long series of observations on the histological changes in the pituitary which result from interference with the function of other ductless glands. The experiments were done on cats, dogs, rabbits and rats. The effects of thyroidectomy, parathyroidectomy, castration, pregnancy, pancreatectomy, paranephrectomy, certain combinations of these, and brain incisions, were investigated. The principal findings were as follows: The pituitary always reacts qualitatively in the same way to various endocrine disturbances. Quantitative variations in the reaction of the pituitary depend on the severity of the lesion in other endocrine glands, the duration of the lesion, and the age and species of animal used. All parts of the gland react together. The first phase is an increased functional activity (increase of eosinophils and secretory stage of gland cells). Increase in size being limited by its surroundings, the first phase is followed by structural alterations due to pressure; these are, in order of occurrence, oedema, degeneration, and pigment formation. The reaction to parathyroidectomy is stronger than to thyroidectomy. The secretion of the middle lobe only appears as colloid when increased production and interference with absorption occur. This secretion is removed via the blood stream. The changes undergone by the gland in pregnancy are essentially the same as those produced by other endocrine disturbances, and are not specific. The cysts in the pituitary which are commonly met with in cats and dogs may grow markedly as a result of disturbances in the endocrine system as well as during pregnancy.

Further report of a case of experimental canine gigantism. Putnam,, T. J. and E. B. Benedict. Am. J. Physiol. **85**: 401. 1928.

A sterile extract of the anterior lobe of beef hypophysis has been administered intraperitoneally to a thoroughbred bulldog, in doses up to 55 cc. daily, for about a year. The treated animal has outgrown her litter-mate sister control by 60 to 90 per cent, and shows changes in the bones, skin, nipples and vagina which might be interpreted as acromegaloid. Some of the disabilities of experimental hypopituitarism in dogs can be mitigated by injections of a similar extract.—Authors' Abst.

Presence of melanophore-expanding and uterus-stimulating substance in the pituitary body of early pig embryos. Snyder, F. F., Am. J. Anat. **41**: 399. 1928.

Melanophore-expanding and uterus-stimulating substances are found in the pituitary of pig embryos of 30 mm. crown-rump length; i. e., when the foetus is about one-tenth its length at birth and when the weight of a single gland is roughly 0.05 mgm. This was

determined by perfusing "albino" (hypophysectomized) tadpoles and normal adult frogs and by employing the guinea-pig uterus test for oxytocic action.—W. J. A.

Loosely-bound sulfur in pituitary extracts. Sullivan, M. X. and M. I. Smith. Pub. Health Rep. **43**: 1334-1342. 1928.

Tests were made on 0.25 per cent acetic acid extracts of some thirty-three samples of pituitary powders made according to the U. S. P. X. method of preparing extracts from standard pituitary. The preparations comprised (1) five samples of standard powdered pituitary; (2) a fresh gland extract, 1 cc. of which represented the physiological activity of 7 mgm. of standard powdered pituitary; (3) a sample of a commercial powder which when assayed was found to be of standard potency; (4) two commercial samples physiologically inert; (5) a commercial sample having a slight and almost negligible oxytocic activity; (6) eleven commercial samples of posterior pituitary with different degrees of physiological activity; (7) twelve commercial samples of desiccated anterior pituitary. These extracts were tested, qualitatively, chemically, and physiologically. The physiological criterion mainly relied on was the power to raise the blood pressure when injected intravenously into an anesthetized dog. The chemical test for loosely-bound sulfur was as follows: To 2 cc. of the extract in a small test tube there were added 0.1 cc. of half saturated lead acetate and 1 cc. of sodium hydroxide (usually normal), and the tube was placed in boiling water. Potent extracts begin to brown in 16 seconds and give a black precipitate of lead sulfide within three minutes. Inactive preparations do not show such a coloration. Extracts of commercial posterior lobe, when active, give a positive lead sulfide test, but not as strong, as a rule, as the standard powders. The commercial powders, as a rule, were less active physiologically. Extracts of the anterior lobe, as a rule, give no lead sulfide. In a few cases they gave a slight positive test. Whether the relationship indicated between the physiological test and the chemical test is coincidental or is an indication that the physiological activity of the posterior pituitary is tied up with the presence of highly reactive sulfur compounds remains for further investigation. In either case, the test for highly reactive sulfur should be useful in the isolation and purification of the active principles.—Authors' Abst.

Massive dosage with insulin. Byworth, H. A., Brit. M. J. **1**: 801. 1928.

The author reports a case of diabetes in a man 23 years of age who entered the hospital in a semi-comatose condition. In the course of 36 hours he was given 1,715 units of insulin. Pulmonary tuberculosis and a multitude of small ulcers on his arms and legs

(due likely to insulin injections, the author thinks) were present, which may explain his tolerance to such a huge dosage of insulin.
—H. J. J.

Oral administration of pancreatic and other preparations in treatment of diabetes. Fuller, C. B. S., Brit. M. J. **1**: 798. 1928.

The author worked with several oral pancreatic preparations in an attempt to determine their influence on blood sugar level and the general improvement of tolerance in the patient. Hourly blood sugar estimations were made with the varied preparations, but all with negative results. The first paragraph of his conclusions summarizes best his findings: "From the consideration of the data given it is clear that the administration of oral preparations of pancreas in severe cases of diabetes is a waste of time, and likely to be harmful to the patient by delaying the proper treatment with diet and insulin injections."—H. J. J.

Changes in glycemia seen in depancreatized dogs which carry pancreatic grafts following operation and ingestion of glucose (Variations de la glycémie chez les chiens dépancréatés porteurs d'une greffe pancréatique, apres l'opération et a la suite d'ingestion de glucose). Kepinov, L. and S. P. Dutaillis. Compt. rend. Soc. de biol. **98**: 1193-1195. 1928.

In depancreatized dogs with pancreatic grafts, ingestion of glucose results in a sharp rise in blood sugar followed by a hypoglycemia. This, in turn, is followed by a considerable increase in blood sugar, which does not disappear for several days. The latter rise is not seen in normal animals.—J. C. D.

Answer to Gayet and Guillaumie on the regulation of the internal secretion of the pancreas (Résponse a la note de R. Gayet et M. Guillaumie sur la régulation de la sécrétion interne pancréatique). LaBarre, J., Compt. rend. Soc. de biol. **98**: 859-861. 1928.

The author quotes his previous work to show that, contrary to the above writers, the normal secretion of the islet tissue is under control of the central nervous system, since it ceases as soon as the vagii are cut.—J. C. D.

Hypertrophy (adenoma?) of the islands of Langerhans with associated hypoglycemia. Norris, G. W. and W. U. McClenahan, Proc. Assoc. Am. Physicians, May, 1928. Abst., J. A. M. A. **91**: 50. 1928.

A colored man, aged 41, gave a history of periodic attacks of loss of memory of a gradual onset, which generally lasted one and a half hours, occurred usually at midday and were relieved by taking food. Between attacks he was free of symptoms. The physical examination was essentially negative on admission. The following

day the patient fell into coma from which he never recovered. The blood sugar showed 40 mgm. of sugar per 100 cc. on this day. He developed terminal broncho-pneumonia and died seventy-two hours after admission. The spinal fluid examination was negative, except for a low sugar content (20 mgm. per 100 cc. of fluid). In spite of the administration of dextrose by gavage, entercylsis and intravenously, the hypoglycemia persisted and sugar determinations were 40, 46 and 38 mgm. per 100 cc. on the three successive days. At autopsy a partially encapsulated, vascular nodule, measuring 17 by 5 by 10 mm., was found in the pancreas, composed of cells similar in structure and arrangement to those of the islands of Langerhans, and associated with a generalized hyperplasia of the islands throughout the pancreas. The suprarenals and pituitary were negative. There was no evidence of metastasis, and the eosin and hematoxylin stains of the liver failed to show a significant decrease in its glycogen content. The analysis of both the pancreas and the tumor tissue for their insulin content was attempted, but was unsuccessful. The finding of a lesion of the pancreatic islands in this case, associated with hypoglycemia and a very significant history, would seem to add further evidence toward the recognition of a new disease entity.

Carcinoma of the islands of the pancreas. Thalhimer, W. and F. D. Murphy. J. A. M. A. **91**: 89-91. 1928.

After two and a half years of gradually increasing severity of symptoms, a patient developed a state of almost constant semi-stupor, accompanied by frequent convulsions and marked hypoglycemia, until death followed, apparently from exhaustion. At necropsy, the only significant pathologic lesion found was a small primary tumor of the pancreas. Its microscopic appearance indicated that it originated from the cells of the islands of Langerhans, and that the tumor is either a carcinoma or a low grade of malignancy, or else an adenoma. It is believed that the active secretion of insulin by these tumor cells caused a hyperinsulinism which resulted in hypoglycemia and, finally, in death.—Authors' Abst.

The direct stimulation of the islands of Langerhans by adrenin (Action stimulante directe de l'adrénaline sur les ilots de Langerhans). Zunz, E. and J. LaBarre. Compt. rend. Soc. de biol. **98**: 858-859. 1928.

The donor (dog) was decapsulated and the recipient depancreatized. Then the pancreatic circulation of the donor was connected with the carotid-jugular circulation of the recipient. Injection of adrenin chlorhydrate in the recipent resulted in a hypoglycemia.—J. C. D.

The effect of ligation of the common bile duct upon the appearance of tetany in thyroparathyroidectomized dogs. Brougher, J. C., Am. J. Physiol. **86**: 39-41. 1928.

Ligation of the common bile duct with or without cholecystectomy prevented the appearance of parathyroid tetany in 5 dogs. In 3 mild tetany occurred. This delay in the appearance of tetany may be attributed to one or all of the following factors: (a) a lessened excretion of calcium from the body by way of the bile; (b) increased absorption of calcium from the gut because of the absence of the alkaline bile acids, which precipitate calcium; (c) depression of the nervous system by the absorbed bile.—R. G. H.

The effects of selective solar irradiation on the parathyroid glands of chicks. Higgins, G. M. and C. Sheard, Am. J. Physiol. **85**: 299-310. 1928.

Studies are reported on the influence of selective solar irradiation on the parathyroid glands of chicks. The chicks were kept within doors behind amber, blue, ordinary glass and vitaglass, which transmit known portions of the sun's spectrum. The basic diet used throughout the experiment was the Wisconsin all-mash ration. Half of the chicks under each filter were fed the basic diet alone, while the other half were fed the basic diet and 2 per cent by weight of cod-liver oil. All the chicks of each pen thrived equally well during the earlier months of the experiment; signs of weakness of the legs did not develop until they were five months old. Enlargement of the parathyroid glands was recognized within the first few weeks in chicks growing under amber and blue glass; this enlargement was due to hyperplasia rather than hypertrophy. The 2 per cent of cod-liver oil added to the basic diet serves to maintain a more nearly normal sized gland even in the longer wave lengths of sunlight. Both the longer and the shorter wave lengths of sunlight are essential to the maintenance of normal parathyroid glands. Regression of the cell columns is manifested early; the cause is undetermined. Cysts accompany the retrogressive processes that ensue within the gland. These cysts are of two types. One is walled off from the remaining portion of the gland by definite columnar epithelium, while the other is enclosed by a series of concentrically arranged flattened cells. There was no organic indication either in blood calcium, blood phosphorus or general activity that such parathyroid hyperplasia had arisen.—Authors' Abst.

Tissue changes in parathyroid tetany and in guanidine poisoning. Larson, E. and L. A. Elkourie. Am. J. Physiol. **85**: 387-388. 1928.

A series of dogs, cats and rabbits was injected subcutaneously with fatal doses of guanidine hydrochloride. Three dogs were thyroparathyroidectomized and allowed to die in an acute attack of tetany. Both of these series of animals were autopsied immediately

and tissues saved for microscopic examination. Any gross changes were noted. The tissues of the animals dying of guanidine poisoning showed the following changes: The kidneys presented a condition of simple necrosis of the tubules, with the glomeruli little affected and no congestion. The liver, in every case, exhibited fatty degeneration at the periphery of the lobules and simple necrosis at the center. The spleens showed no striking changes. The adrenals were in varying stages of simple necrosis. The testes and epididymides appeared normal. Examination of these tissues from the dogs dying of parathyroid tetany revealed the following changes. Both the glomeruli and the tubules of the kidneys were greatly congested, with necrosis of the cells of the tubules. The livers were congested to a great degree. Simple necrosis of the hepatic cells were apparently little affected. The spleens, in every instance, were immensely congested with the presence of blood pigment. The adrenals were likewise congested. The various areas presented varying degrees of necrosis. There were marked differences between the microscopic findings in the viscera of animals dying of parathyroid tetany and those dying of guanidine poisoning.—Authors' Abst.

Interrelations of calcium, phosphorus and sugar in parathyroidectomized dogs. Reed, C. I., Am. J. Physiol. **85**: 402. 1928.

In an effort to explain the nature of the adaptation occurring in latent tetany when animals survive without restoration of normal proportions of calcium and phosphorus, it was noted that ingestion of 2 gm. per kgm. of glucose frequently relieved dogs from an attack of tetany within 30 minutes to 2 hours. In controlled dextrose tolerance tests it was found that during an attack of tetany there was decreased tolerance, which was usually at the peak at the end of 2 hours, while in normal dogs and those not in tetany this point was found to occur at about the end of the first hour. The fasting blood sugar level was not affected by parathyroidectomy. All fractions of phosphorus were decreased in concentration from 10 per cent to 50 per cent. Calcium was not greatly affected in normal dogs, but after operation there was a tendency to fluctuations, with ultimate diminution. The action was usually completed in two hours. The diminuation in concentration of inorganic phosphorus was usually sufficient to raise the Ca:P ratio to a higher figure and relief from tetany may, at present, be assigned to this factor. In order to determine the effect of a decreased blood sugar concentration, insulin was injected subcutaneously. In both normal and operated dogs, with and without tetany, dextrose and inorganic phosphorus concentrations were lowered. In tetany the calcium concentration tended to fluctuate, while in normal and operated dogs not in tetany this factor was invariably increased. In every case of tetany the net result of insulin injection was an increase of the Ca:P ratio, which, if great enough, resulted in relief from tetany.

—Author's Abst.

The thyroid and pregnancy (La thyroid au cours de la grossesse). Bernard, W., Rev. franç, d'endocrinol. **5**: 395. 1927.

The author records his personal observations in two parts: (1) Histological changes in the thyroid of the dog during pregnancy, and (2) the effect of partial thyroidectomy on pregnancy in guinea pigs. He shows there is cyclic change in the glandular structure; in dioestrus the follicular cells are large and the follicle is well filled with colloid; three days after coitus there is in many cases a change in the number and volume of vesicles; at thirty-two days the follicular cells are much changed, the follicle itself becoming much enlarged; at forty-three days the cells and follicles have regained much of their dioestrus appearance, while the interstitial cells have multiplied rapidly; a few days after delivery the thyroid returns to the normal dioestrus appearance. The author reports that partial thyro-parathyroidectomy in guinea pigs prolongs the gestation period as much as eight days.—B. Cunningham.

Thyroid disease. An experimental study. Cooksey, W. B. and M. S. Rosenblatt. Arch. Int. Med. **42**: 1-13. 1928.

The question of excessive thyroid secretion in exophthalmic goiter and allied diseases is discussed, and the various claims for and against hyperthyroidism are presented. Feeding experiments were conducted in which various types of goitrous glands from human beings were fed to tadpole larvae. There is evidence from these experiments that thyroid glands from clinically active cases of goiter contain more active thyroid principle per unit weight than the normal thyroid. Other goitrous glands contained less active principle by this biologic test, and the amounts were directly proportional to the clinical activity of the patient. Old non-toxic adenomas contained less active principle per unit weight than normal, while one gland which had had much roentgen-ray treatment and rest also contained less active principle per unit of weight. By these experiments, hypersecretion of the thyroid gland in exophthalmic goiter and other clinical thyrotoxic cases seems definitely proved.—Authors' Summary.

The influence of thyroidectomy on tissue respiration. Dye, J. A. and R. A. Waggener. Am. J. Physiol. **85**: 365-366. 1928.

Plummer, Kendall and others have suggested that the action of the thyroid hormone on the tissues of the body, with accompanying changes in metabolism, is probably catalytic in nature. The very marked delay in the action of thyroxin when injected intravenously into normal or myxedematous patients is hardly in accord with what we know regarding catalytic action. The same objection may be more strongly applied to an assumed drug-like action of thyroxin on the tissues. It occurred to us that this might not be a direct action of the hormone, but an indirect one, in which the intracellular oxi-

dizing systems are the immediate structures involved. To test this assumption experimentally, we have examined certain tissues (heart muscle, kidney cortex, liver and skeletal muscle) from three cretin lambs (twelve weeks after thyroidectomy) and three cretin pups (four and one-half months after thyroidectomy), together with similar tissues from normal animals of the same age and sex (twins and litter mates), for their power to catalyze the oxidation of a-naphthol and dimethyl-paraphenylene-diamine-hydrochloride into indophenol blue. Quantitative determinations were made by an improved colorimetric method. A marked diminution in the power of the tissues from thyroidectomized animals to catalyze the oxidation of the substrate was found in each case, with the exception of liver. Higher values were obtained for this tissue in two of the three lambs, while lower oxidation rates were found in all the tissues examined from the pups without exception. This diminution in amount, activity, potency or other property of the tissue oxidase of cretin lambs, as compared with that of the control animal taken as unity, averaged 15 per cent for heart, 45 per cent for kidney, 20 per cent for liver and 50 per cent for skeletal muscle in 20-minute readings. Lower values were obtained for the pups, in which the tissues were affected more equally; viz., heart, 16 per cent; kidney, 13 per cent; liver, 21 per cent, and skeletal muscle, 9 per cent. These figures compare favorably with the well known fact that basal metabolism may be reduced 30 to 40 per cent below normal in cases of hypothyroidism.—Authors' Abst.

Does the feeding of cod-liver oil prevent tetany in thyroparathyroidectomized dogs? Greenwald, I., Am. J. Physiol. **85**: 376. 1928.

The feeding of cod-liver oil for two or three weeks before thyroparathyroidectomy, and thereafter, did not protect dogs against tetany. This is contrary to the results reported by Jones.

—Author's Abst.

The effect of ultraviolet light upon thyroparathyroidectomized rats. Jung, F. T., Am. J. Physiol. **85**: 383. 1928.

Thyroparathyroidectomized male white rats, kept on a standard diet and weighed daily, were divided into two groups of equal average weight and were exposed daily to the light from mercury-vapor quartz lamps of known strength. The backs of the rats were shaved, and the dosage was approximately fifty times that necessary to produce an erythema in the unhabituated human subject. One group (controls) were shielded from the ultraviolet component of the light by being covered with glass plates. In the first experiment 26 rats were used, and irradiations were begun on the day of the operations. At the end of an arbitrary time limit the mortality,

severity of tetany, and loss in weight were studied; the results agreed in showing a favorable effect of the ultraviolet light. In a second experiment thirteen rats were used, and the irradiations were begun three days before operation. The results were again positive. The conclusions of Swingle and Rhingold from experiments on dogs are therefore corroborated.—Author's Abst.

Seasonal and geographic variations in the iodine and thyroxin content of the thyroid. Kendall, E. C., Proc. Assoc. Am. Physicians, May, 1928. Abst., J. A. M. A. **91**: 121-122. 1928.

Kendall reports the analysis of 100 pounds of fresh hog thyroid glands during the first few days of each month for the past twenty months. In addition, various samples of thyroid material from different parts of the United States and England have been analyzed. It has already been shown by other workers that there is a seasonal variation in the total iodine. The author has confirmed this and found that in January and February 100 pounds of thyroid may contain 14 grams of iodine, while in July and August the iodine increases to about 40 grams, so that there is about 300% variation in the total iodine content. The amount of thyroxin in these glands has also been determined. The importance of considering the compounds which are not thyroxin and which contain iodine is shown by the fact that in the summer, when the iodine content is highest, the proportion of total iodine in the form of thyroxin is not more than 10%. This figure is for almost pure thyroxin (more than 90% thyroxin). In the winter there is a decrease in the amount of total iodine in the form of thyroxin and it may drop to less than 5%, so that from 90 to 95% of the total iodine in the gland is in some other form than thyroxin. The seasonal variation apparently does not occur in the English and Scottish glands. The amount of iodine apparently is uniform. The relationship between the iodine compounds of the thyroid does change greatly when the material is allowed to stand, so that it appears certain that some chemical change can occur in thyroxin when the glands are desiccated or when they have been freshly ground. This modifies the thyroxin in such a way that it is chemically altered and cannot be isolated, but it is still physiologically active. It appears certain that there is another iodine compound in the gland which has the same physiologic activity as thyroxin. This compound is unstable but it is found in the insoluble fraction. The fact that 10% of the total iodine is the maximal amount of thyroxin makes it impossible to account for the activity of desiccated or fresh thyroid by saying that it is all contained in thyroxin. The only conclusion that can be drawn is that some compound is present that is destroyed with alkali, is stable, at least to some degree, to acid, is not thyroxin, but has the physiologic ac-

tivity of thyroxin. Thyroxin appears to be an intermediate form of the active constituent. It must be altered before it can become physiologically active. After this alteration has occurred, it manifests the typical physiologic activity of desiccated thyroid, but it cannot be isolated. It is too unstable. Apparently allowing thyroid material to stand may alter the thyroxin content. This alteration does not consist merely in a detachment of the thyroxin from the protein. If that were so, then the thyroxin could be recovered. It must be some more deep-seated modification, and may possibly be the attachment of a second hydroxyl group to the thyroxin.

Observations on the antagonism between thyroid and thymus in controlling body weight (Recherches sur l'antagonisme du thymus et du corps thyroide au point de vue de leur influence sur le poids du corps). Križenecky, J., Compt. rend. Soc. de biol. **98**: 1031-1033. 1928.

In pigeons fed with thyroid there is a marked reduction of body weight. With thymus the reduction is slight. If thymus and thyroid are fed together, the former antagonizes the effect of the thyroid and there is only a slight reduction.—J. C. D.

Concerning the influence of hyperthyroidism and hyperthymism on the maturation, growth and pigmentation of the feathers in full grown fowls (Ueber den Einfluss der Hyperthyreoidismus und des Hyperthymismus auf Reifung, Wachstum und Pigmentierung des Gefieders bei ausgewachsenen Huehnern). Križenecky, J. and J. Podhradsky. Arch. f. Entwcklngsmechn. d. Organ. **112**: 577-593. 1927.

Pure bred fowls of both sexes were fed thyroid and thymus separately and in combination. Hyperthyroidism hastened and stimulated moulting and feather growth, and produced depigmentation and partial albinism. These effects were uninfluenced by hyperthymism, nor did the latter produce effects of its own. The only sign of thyroid feeding that appeared in the moult following cessation of the latter was its incomplete patchy character. Partial albinism was transitory, occurring only while hyperthyroidism was maintained.—H. B. Torrey.

Further experiments on the influence of the thyroid and the thymus on feather development in poultry (Weitere Versuche ueber den Einfluss der Schilddruese und der Thymus auf die Entwicklung des Gefieders bei den Huehnerkuecken). Križenecky, J. and M. Nevalonnyj, Arch. f. Entwcklngsmechn. d. Organ. **112**: 594-639. 1927.

Four races of pure bred fowls, that varied somewhat in their responses to thyroid, were used. In general it appeared that hy-

perthyroidism hastened the appearance of contour feathers; produced albinism that first affected the downy basal portions of the feathers resembling in this respect the feathers of the alpine crow (**C. cornix**) and, according to the authors, for the same reason; changed both structure and pigmentation of the feathers in both sexes toward the female type—the latter being regarded rather as a product of constitutional hyperthyroidism than the direct result of ovarian activity. Contrasted with these results were those associated with hyperthymism which, while not influencing the form and sexual characteristics of the feathers, inhibited somewhat the feathering out of the chicks and intensified the plumage pigmentation.—H. B. Torrey.

Experiments on the function of the thyroid and the thymus in the regeneration of plucked feathers (Versuche ueber die Funktion der Threoidea und der Thymus bei Neubildung des ausgerupften Gefieders). Križenecky, J., M. Nevalonnyj and I. Petrov. Arch. f. Entwcklngsmechn. d. Organ. **112**: 640-659. 1927.

Desiccated thyroid and thymus, separately and in combination, were fed to pigeons some of whose dorsal feathers had been plucked. Neither the rate of regeneration nor the form of the feathers replacing the old ones was affected. Hyperthyroidism stimulated moulting, hyperthymism to a less extent. In combination, hyperthyroidism plus hyperthymism produced a greater effect than the sum of their effects, separately.—H. B. Torrey.

The prevention of fatal parathyroid tetany in thyroparathyroidectomized dogs, by the administration of thyroid hormone. Kunde, M. M., R. Oslund and R. Kern. Am. J. Physiol. **85**: 387. 1928.

Dogs in a hyperthyroid condition may be thyroparathyroidectomized and fed a diet containing 200 to 400 grams of meat daily without the occurrence of fatal parathyroid tetany, provided the hyperthyroid condition is maintained. The blood calcium and phosphorus are normal in these dogs, as is also renal function.

—Authors' Abst.

Influence of internal secretions and of trephones on phagocytosis. Morgulis, S. and B. A. Schatzillo. Am. J. Physiol. **85**: 396. 1928.

Phagocytosis in normal serum as well as in serum of castrated or thyroidectomized animals is increased through the addition of trephones. The addition of trephones to thyroxin increases the phagocytosis of normal serum or of serum from thyroidectomized animals. The phagocytosis of serum from castrated animals is little altered from that of normal. Phagocytosis is diminished both after thyroidectomy or after parathyroidectomy. The phagocytic reaction in vivo of parathyroidectomized dogs is lowered. Tre-

phones exert no effect on the placental hormone, and the placental hormone has practically no influence on phagocytosis. Under the influence of trephones not only is the number of phagocytosing cells increased, but the quantity of material ingested is likewise markedly increased.—Authors' Abst.

Basal metabolism. III. Influence of work with special reference to the thyroid gland. Smith, J. H., Arch. Int. Med. **42**: 47-52. 1928.

In fifty subjects the basal metabolic rate was determined, followed by a determination of the rate as influenced by imposing a load of one-twelfth the subject's body weight. All subjects with toxic goiter and with abnormally high basal rates (twelve) showed an increase in rate under the load varying from 22 to 64% of the subject's normal basal rate, and averaging 36.9%. The average of thirty-eight other cases was 14.1%. Two of the three subjects with toxic goiter and with basal rates under plus 20 who are taking compound solution of iodine showed a rise under the load suggestive of the thyroid hyperfunctional state; one did not show any rise above the normal of 20%. In three cases in which the basal rates were above plus 20 and in which there was no rise above 20%, none of the patients was found to have toxic goiter. Of the subjects with borderline basal rates not showing a rise of more than 20%, only the two patients taking compound solution of iodine were found to have toxic goiter. No fixed ratio appeared to exist between the increased basal rate of subjects with toxic thyroid and their abnormal response to work further than that the cost of work is higher than normal. An increased response to work did not appear to be a specific thyrotoxic phenomenon.—Author's Summary.

The effect of thyroid therapy on children. Topper, A. and P. Cohen, Am. J. Dis. Child. **35**: 205. 1928.

The effect of thyroid therapy was studied in 14 children. In 4 patients with subnormal thyroid activity as evidenced by subnormal basal metabolism and clinical symptoms of hypothyroidism, thyroid in small or moderate doses promptly brought the basal metabolic rate to the normal level, where it remained even after the thyroid therapy was discontinued. In one child with a normal metabolism 12 grains of thyroid extract by mouth with 5 mgm. of thyroxin caused a transient increase in the pulse rate and basal metabolism. In 9 children with normal basal metabolic rates doses up to 15 grains daily did not increase the metabolic rate. A marked increase in growth was observed in 4 of these children. Since thyroid extract in relatively large doses does not seem to have any effect on the basal metabolic rate of normal children but has a stimulative effect on growth, one should question whether this rate should

be the criterion of the effects of thyroid therapy in normal children. The action of thyroid on normal children differs from that on normal adults. On this basis, the authors offer a theory to the effect that thyroid is a normal catalyst which increases the phase of metabolism dominant in the individual anabolic or growth processes in the child and katabolic or oxidative processes in the adult. Thyroid affects the growth processes of the normal child but has no effect on the basal metabolic rate, whereas in the adult where the growth processes are complete, the metabolic rate is changed.

—M. B. G.

Iodine compounds. Their selective absorption by the hyperplastic thyroid gland in the dog. Van Dyke, H. B., Arch. Int. Med. **41**: 615. 1928.

An attempt was made by acute experiments to determine quantitatively the rates at which the hyperplastic thyroid gland of the dog selectively absorbs various iodine compounds. Thyroxine iodine was very slowly taken up, while free iodine was absorbed relatively more rapidly. Iodate iodine was bound quickly by such glands but apparently not so quickly as iodide iodine, which is selectively absorbed by the hyperplastic gland more rapidly than any of the iodine compounds studied. The selective absorption of iodine, iodate and iodide iodines was unaffected by complete bilateral ligation of the suprarenal glands six or seven hours previously.—Author's Abst.

Ophthalmoplegia in Graves' disease. Wedd, A. M. and H. H. Permar. Am. J. M. Sc. **175**: 733-740. 1928.

A case of recurrent Graves' disease is reported in which the symptoms begin with visual disturbances due to external ophthalmoplegia, and death resulted during a thyroid crisis. The postmortem examination revealed changes in the thyroid gland believed to represent an exhausted state. There were degenerative changes in the adrenal cortex, while the thymus showed an unusual degree of degeneration. The ophthalmoplegia in the case studied is believed to have been a part of the Graves' syndrome and not an expression of an independent symptom complex.—Authors' Summary.

Proof that desiccated thyroid increases sugar utilization while commercially prepared thyroxin and other iodine compounds do not. Wickwire, G. C., L. D. Seager and W. E. Burge. Am. J. Physiol. **85**: 412. 1928.

One hundred milligrams of desiccated thyroid containing 0.55 mgm. of iodine were dissolved in 100 cc. of 0.1% dextrose solution. Similarly amounts of thyroxin, calcidine, potassium and sodium iodides containing the same amount of iodine as the 100

mgm. of desiccated thyroid were added to other 100 cc. portions of 0.1% dextrose in beakers. One portion of sugar solution to which nothing was added served for control. Two gold fish with a combined weight of approximately 5 grams were introduced into each beaker. Air was kept bubbling through the sugar solutions to insure an adequate supply of oxygen to the fish. Sugar determinations of the solutions were made immediately and after thirty hours according to the method of Benedict. None of the iodine compounds affected sugar utilization except the desiccated thyroid. This produced an increase of more than 50% over the control. Several experiments similar to the preceding were done with comparable results. Much larger quantities than the above of thyroxin, calcidine, potassium and sodium iodides were used and in no case was utilization increased above the control, while smaller quantities of desiccated thyroid gave a marked increase in sugar utilization.—Authors' Abst.

Annual Index

Authors

Abderhalden, E. (Hartman): Comparison of the action of natural and synthetic thyroxin 122
— (Wertheimer): Relation of thyroxin action to sympathetic nervous system.....122
Abel, J. H.: Some recent advances in knowledge of ductless glands 213
Abramowicz, I.: On bitemporal contraction of visual field in pregnancy 698
Adamson, J. D.: The liver as the organ of sanguinification.....359
Addair, John (Chidester): Influence of pineal feeding on metamorphosis 791
Aderman, N.: cf. Jonsson.....508
Aldrich, T. B.: cf. Kramm.358, 699
Allan, F. N.: Diabetic acidosis and leucocytosis 111
Altenberger, H. (Stern): Quantitative estimation of posterior pituitary lobe secretion in cerebrospinal fluid of epileptic.820
Altmann, E.: Cyclic changes in the ovary of the mole.....355
Altnow, H. O.: Changes in eyeground in vascular disease and in related conditions 360
Anders, J. M. (Jameson): Adiposity and other etiological factors in diabetes mellitus.....223
Aoki, K.: Clinical and experimental studies on the effect of quinin upon the nitrogen metabolism of hyperthyroidism..369
Archer, B. W. C.: cf. Worcester-Drought 359
Arndt, H. J.: Topography of parathyroids in swine 230
Arnell, O.: Influence of sodium salt of barbital on effects of adrenin 209
Arnett, J. H.: Addison's diseases and diabetes mellitus occurring simultaneously 89
Arnovljevitch, V.: cf. Chahovitch 506
Aron, M.: Testicular grafts in Triton. Fresh experimental evidence that sex cells do not control secondary sex characteristics 695
Arquin, S. F.: Modification of adrenalin effect with functional status of stomach.....209
Artundo, A.: Glycemia, glycogen and the action of insulin in decapsulated rats 220
Ascheim, S. (Zondek): Diagnosis of pregnancy by detection of hormone in the urine 513
— cf. Zondek 217
Aschner, B. (Lahm): Handbuch der inneren sekretion.....688
Asher, L. (Guggenheim): Handbook of internal secretions...687
Atkinson, Dorothy (Lisser and Shepardson): Pronounced exophthalmos in adenomatous goiter without hyperplasia....680
Aub, J. C. (Bauer, Ropes and Heath): Relation of thyroid gland to calcium metabolism..233
Aubertin, E.: cf. Mauriac.....527
Auger, L.: cf. Jung.....224
Austin, W. C. (Matthews): Calcium content of gastric juice..119
Avel, M.: Influence of transplantation on sex character of earth-worms 214

Bachem, A.: cf. Fisher.....335
Bailey, P.: cf. Horrax.....368
Barthels, C.: Symptoms and treatments of malignant goiter 704
Bauer, W.: cf. Aub.....233
Baumgartner, E. A.: Parathyroid in treatment of tropical sprue 120
Beaumont, J.: Changes in urogenital apparatus of female Triton cristatus following testicular grafts 513
Bell, Marion: cf. Blatherwick..522
Bellerby, C. W.: cf. Parkes....516
Bencan, C. (Champy, Keller): The female sex hormone.....514

Benedict, E. B.: cf. Putnam...822
Benetato, Marie: cf. Nitzecu...359
Benoit, J.: Over-masculinity in the cock. New evidence favoring the theory of a quantitative action of the sex hormone....514
Berberich, F.: cf. Jaffee (Book Review) 686
Berberich, J. (Fischer-Wasels): Handbuch der inneren Sekretion (Book Review).....686
Berglund, H. (Medes and Lohmann): Effect of hypercalcemia on creatin output in myasthenia gravis 367
Berman, L.: Glands regulating personality—a study of glands of internal secretion in relation to types of human nature (Book Review) 689
Bernard, W.: Thyroid and pregnancy 828
Bernardbeig, J. (Sendrail): Influence of thyroidectomy on the absorption of water by the tissues 533
Bertram, F.: The peripheral control of blood sugar by drugs 694
Biassotti, A.: Influence of suprarenals on blood pressure regulation 505
Binet, L. (Giroud): Glutathione and the adrenals.....505
Bircher, E.: Langhan's proliferating goiter 122
Blatherwick, N. R. (Sahyun): The effect of cobalt on insulin hypoglycemia in rabbits.....111
— (Sansum, Bell, Hill): The insulin requirements on various diets 522
Bloch, E.: Raynaud's disease and the pituitary.....107
Blumgart, H. L.: cf. Gargle....699
Bogan, I. K.: cf. Morrison.....115
Boldyreff, E. B.: Secretion of pancreatic juice—a glycolytic factor in blood 522
Bonilla, E. (Moya): Blood sedimentation in Addison's disease 351
— (Velasco): Hyperthyroidism caused by pyelitis 534
Boothby, W. M. (Sandiford, Sandiford and Slosse): Effect of thyroxin on respiratory and nitrogenous metabolism of normal and myxedematous subjects 234
Bortz, Edward L.: Hypersensitivity to insulin.....501
Bourne, A. (Burn): Dosage and action of pituitary extract and of ergot alkaloids on uterus in labor. Action of epinephrine.107
Bourquin, H.: Further observations on diuretic substance of experimental diabetes insipidus.820
— Studies on diabetes insipidus II. Diuretic substances, preliminary observations 97
Bowman, K. M.: Endocrine and biochemical studies in schizophrenia 817
Boyd, Gladys L: Course and prognosis of diabetes mellitus in children 111
Brace, W. M.: Insulin and carbohydrate tolerance.....360
Brainerd, H. G.: cf. Brousseau Book Review.....685
Bram, I.: Graves' disease redefined 190
— Relationship of diseased tonsils to goiter.....234
— Tolerance for quinine in exophthalmic goiter 705
Brambell, F. W. R. (Parker): Changes in ovary of mouse following exposure to x-rays. III. Irradiation of non-parous adult.214
— cf. Parkes.....516
Brehme, T. (Gyorgy): Metabolic effect and clinical application of Collip's parathyroid hormone 230
Brinkworth, D. J. T.: Cf. Dickens 100
Brougher, J. C.: Effect of ligation of common bile duct upon appearance of tetany in thyroparathyroidectomized dogs....826
— The treatment of parathyroidectomized dogs with cod liver oil.....532
Brouha, L. (Simonnet): Experimental and clinical facts concerning follicular hormone.... 99
— — Studies on distribution of follicular hormone in body 215
Brousseau, Kate (Brainerd): Mongolism. A study of physical and mental characteristics of mongolian imbeciles. Book Review 685
Brown, A. L.: Endocrines in general medicine. Book Review..690
Brown, T. B.: Hypothyroidism as cause of intractable constipation 235
Bruno, A: Acetates in normal and diabetic blood.....220

Buchbinder, W. E. (Kern): Experimental obstructive jaundice. II. Modification of the thyroid tetany mechanism in jaundice. 532
Bugbee, Edwin P. (Kamm): Recent progress in investigation of posterior lobe of pituitary. . 671
— (Simond): Diuretic - antidiuretic effect of pressor principle of posterior lobe of pituitary gland 698
— cf. Kamm 358. 699
Burge, W. E. (Wickwire, Estes and Seager): Effect of adrenalin on sugar metabolism 157
— (Estes and Wickwire): Study of substance in desiccated tissues which increases sugar utilization more than insulin 700
— cf. Wickwire 834
Burgess, N.: Calcium metabolism in skin diseases 694
Burn, G. H.: cf. Bourne 107
Burn, J. H.: Methods of biological assay. Book Review 690
Burns, Frances H.: cf. Riddle . . 104
Burns, J. H.: cf. Coward 356
Busquet, H.: Production of male characteristics in capons and senile cocks by injection of serum from young males 215
Byworth, H. A.: Massive dosage with insulin 823

Cadenhead, F. G.: cf. Miller 537
Cahane, M.: cf. Parhon 214
Campanacci, D.: cf. Ponticcaccia . 116
Campbell, D. L.: cf. Geiling 113
Canciulesco, M. (Herman and Hirsch): Latent malaria and adrenin 505
Cantarow, A. (Dodek and Gordon): Calcium studies in jaundice. With special reference to effect of parathyroid extract on distribution of calcium 118
Carlson, A. J.: cf. Kunde 126
Carrasco-Formiguera, R. Synthalin in diabetes 112
Carson, D. A.: Creatine excretion in artificial hyperthyroidism . . 534
Castiglioni, G.: Alterations in the homoplastic grafts of endocrine organs 511
Caulaert, V.: cf. Mestrezat 520
Chahovitch, X. (Arnovljevitch and Vichnjitch): Temperature control and the adrenals 506
— (Vichnjitch): Influence of castration on metabolism 695
— cf. Giaja 351
Chaikoff, I. L. (Weber): Effect of glucose on the ketone body excretion in fasting depancreatized dogs 360
— — The formation of sugar from fatty acids in the depancreatized dog injected with epinephrine. 522
Champy, C. (Keller): Uterine and mammary development following injection of the ovarian hormone 355
— cf. Bencan 514
Chidester, F. E.: cf. Addair 791
Clark, G. A.: The origin of the glucose in the hyperglycemia induced by pituitrin 519
Clark, G. H.: The influence of the vagus on the islets of Langerhans. III. Further experiments in vagotomy 522
Clute, H. M.: cf. Smith 375
Coelho, E.: Posterior pituitary lobe extract: its action on water excretion in normal cases, cases with diabetes insipidus, and cases with sclerotic kidneys 699
Coelho, E. V. (Oliveira): Relations between the internal and external secretions of the pancreas 523
Cohen, P.: cf. Topper 833
Cole, W. H. (Womack): Thyroid infections and toxemias 369
— cf. Lehman 121
— cf. Womack 773
Combes, T. J. C.: The influence on glucose solutions of insulin and of muscle from a normal and a diabetic dog 523
Connor, C. L.: cf. Gordon 222
Cooksey, W. B. (Rosenblatt): Thyroid disease. An experimental study 828
Cooper, Eugenia R. A.: Histology of more important endocrine organs at various ages . . 685
Corey, E. L.: Survival period in pregnant and lactating cat following adrenal extirpation 351

Cori, C. F. (Cori): Fate of sugar in the animal body. VII. Carbohydrate metabolism of adrenalectomized rats and mice...209
—— Fate of sugar in the animal body. IV. Tolerance of normal and insulinized rats for intravenously injected glucose and fructose. V. A seasonal occurrence of ketonuria in fasting rats accompanied by changes in carbohydrate metabolism 220
—— Influence of epinephrine on the carbohydrate metabolism of fasting rats.....521
Cori, Gerty T.: cf. Cori.....209, 220, 521
Corner, G. W.: Relation between menstruation and ovulation in the monkey 100
Corsonello, P.: Sedimentation velocity of red corpuscles and the effect of various gland extracts 97
Costello, J. P.: Thymic enlargement as cause of atelectasis..232
Courrier, R.: Effects of ingestion of thyroid upon the thymus, testicle and thyroid.....705
— (Duboucher and Pouget): Pseudo-pregnancy produced by the persistence of a corpus luteum spureum.....514
Coward, Katherine H. (Burns): The variation in the unit of the oestrus-producing hormone ...356
Crosbie, A. H. (Smith): Primary tumor of the suprarenal capsule with especial reference to adrenal virilism 506
Curschmann, H.: Myxedema and Erb's familial muscular dystrophy 235
Cushing, H.: cf. Davidoff.....108
Dale, H. H. (Richards): Depressor (vaso-dilator) action of adrenalin 210
Daly, P. A.: cf. Strouse.....227
Davidoff, L. M. (Cushing): Studies in acromegaly VI. The disturbance of carbohydrate metabolism 108
Davidson, J. R.: Nephrosis of thyroid origin 369
Dayton, T. R.: Pars intermedia of the human hypophysis.....217
De Courcy, J. L.: Exophthalmic goiter 235
— Preoperative use of compound solution of iodine in exophthalmic goiter 369
Decourt, J.: cf. Loeper.....813
Delbaere, L. J.: Blood sugar, adrenaline and sympathetic nervous system. A test for excitability of sympathetic..... 89
De Leo, S.: Sympathetic suprarenal lesions in some symptomatic depressive syndromes... 90
De Quervain, F. (Smith): Iodine content of blood in ordinary goiters and in cretinism.....177
De Vigneaud, V. (Jensen and Wintersteiner): Studies on crystaline insulin. III. Further observations on crystallization of insulin and on nature of sulphur linkage. Isolation of crystine and tryosine from hydrolized crystaline insulin....523
Dickens, F. (Dodds and Brinkworth): Ovarian hormone in water soluble form.....100
Dickson, W. C. C.: cf. Worcester-Drought 359
Dodds, E. C.: cf. Dickens.....100
Dodek, S. M.: cf. Cantarow.....118
Doe-Kulmann, L. (Stone): Mental development of children exhibiting somatic signs of puberty praecox 98
Dohrn, M.: Is the Allen-Doisy test specific for the female hormone? 514
— cf. Steinach 517
Doisy, E. A.: cf. Kahnt.....760
— cf. Thayer 769
— cf. Veler 697
Donaldson, J. C.: Adrenal gland in wild gray and albino rat: Corticomedullary relations....506
— The adrenal gland in pregnancy: Cortico-medullary relations in albino rat.....506
Dowgiallo, N. D.: Correspondence between subperitoneal nervous plexus and abdominal paraganglia 351
Downs, W. G.: Studies in causes of dental anomalies.....109
Doxiades, L. (Pototzky): Significance of cardio-vascular methods of investigation in diagnosis of mongolianism and myxedema in children.....236

Dragstedt, C. A. (Huffman): Comparative sensitiveness of blood pressure and intestinal motility to epinephrin.....506
— — Comparative effect of epinephrin upon blood pressure and intestinal motility in man.....813
— — Comparative effect of epinephrin upon blood pressure and intestinal motility in the dog.....691
— (Wightman): Observations on hemodynamic effect of epinephrine in unanesthetized dogs 210
— (Wightman and Huffman): The hemodynamic action of minimal effective doses of epinephrin in the unanesthetized dog 507
Duboucher, H.: cf. Courrier....514
Durant, R. R.: The blood pressure of adrenalectomized rats.691
— (McNinch): Vasomotor responses to perfused adrenalin in the unanesthetized dog 813
Durrant, E. P.: Effect of desiccated thyroid on growth of guinea pig 705
— Relation of parathyroidectomy to voluntary activity in the white rat 703
— Relation of hysterectomy to voluntary activity 100
Dutaillis, S. P:. Kepinov.....824
Dye, J. A. (Waggener): Influence of thyroidectomy in tissue respiration 828

Eidelsberg, J.: Hypopituitarism. Summary of observations in twenty-seven cases followed seven years 109
Eisler, B.: cf. Schittenhelm....375
Elkourie, L. A.: cf. Larson.119, 826
Elliott, C. A.: Control of hyperthyroidism by thryroidectomy.123
— Results of thyroidectomy for hyperthyroidism as indicated by examination a year or more following operation..236
— (Nadler): Management of diabetes mellitus associated with pulmonary tuberculosis 221
— (Starr and Nadler): Glycemia as a practical guide in the treatment of diabetes mellitus 221
Engle, E. T.: Gonad stimulating hormone of anterior pituitary and heterosexual ovarian grafts 215
— Pregnancy following superovulation in mouse.....216
— (Mermod): Effect of daily transplantation of anterior lobe on course of pregnancy in rat and mouse 821
Enriquez, P. (Robuschi): Functional relation between endocrine glands and fracture of bones 98
Eshleman, C. L.: Long-standing hyperthyroidism with spontaneous subsidence 237
Estes, A. M.: cf. Burge...157, 700
von Euler, U.: Hyperadreninemia in fever..... 90
Evans, J. I.: cf. Hartman.....692
Evvard, J. M.: Iodine deficiency symptoms and their significance in animal nutrition and pathology 539

Faure, W.: cf. Steinach.....517
Fellegi, G.: Insulin and hypercholesterolemia 523
Ferreira, de M.: Effect of intramuscular injections of adrenin on the gastrocnemius of a decapsulated frog 507
Fertik, J. M. (Majanz and Monossohn): Endocrinological formulae in children at various age periods 512
Fieschi, A.: Action of adrenal cortex on growth 90
Firestone, F.: Estrogen, a new sex hormone: Its clinical use with case reports.....151
Fischer, A. W.: cf. Jaffe (Book Review) 686
Fischer-Wasels, B.: cf. Berberich (Book Review).....686
Fisher, N. F. (Larson and Bachem): Effect of x-rays on adrenal glands 335
— cf. Larson 519
Fitz, R.: Clinical problems in management of diabetes with review of four fatal cases....222
Flack, R. A.: cf. Mason.....363
Flemion, Florence: cf. Riddle..203
Florentin, P.: Vater Pacinian corpuscles in the parathyroid glands of guinea pigs.....704

Fontes, G. (Thivolle): Insulin does not increase binding power of blood cells for glucose, regulation of this theory of glycemia.....701
Fontes, J.: cf. de Mira.....814
Foshay, L.: Insulin reactions...112
Frank, E.: Synthetic substance (synthalin) with insulin action 112
Frank, R. T. (Goldberger): Clinical data obtained with the female sex hormone blood test.216
Frazier, C. H. (Mosser): End-results from surgical treatment of hyperthyroidism.....370
Freudenberg, E.: Adrenalin and muscle tonus 352
Fuller, C. B. S.: Oral administration of pancreatic and other preparations in treatment of diabetes 824

Gans, H. M. (Miley): Ergographic studies on adrenalectomized animals 91
Gardiner-Hill, H. (Smith): Influence of disease of thyroid on menstruation 370
Gargle, S. L. (Gilligan and Blumgart): Antidiuretic effect of the oxytocic and pressor principles of the extract of the posterior lobe of the pituitary...699
Garot, L.: cf. Plumier-Clermont.212
Gayet, R. (Gayet and Guillanmie): Vasomotor action of adrenin on muscle.....211
— (Guillaumie): Demonstration by pancreatic transplantation of control of internal secretion of pancreas through hormones 222
— — Regulation of glycemia in diabetic dogs by transplantation of varying amounts of pancreas...524
Gayet, T.: cf. Gayet.....211
Gavrila, J.: cf. Uitzescu.....364
Gehrke, M.: cf. Schoeller.....537
Geiger, Sara: Some results of endocrine therapy in behavior disorders of children: A preliminary report 98
Geiling, E. M. K. (Campbell and Ishikawa): Effect of insulin on hypophysectomized dogs...113
— cf. Supneiwski 118
Geldrich, J.: Experiments in myxedema in childhood.....237
Gesell, A.: Infancy and human growth (Book Review).....689
Giaja, A.: cf. Giaja.....351
Giaja, J. (Chahovitch and Giaja): Absence of fever in infected rats deprived of adrenal glands 351
Gibson, A. H.: Parathyroid extract in infantile tetany, report of a case.....231
Gibson, R. B.: Latent tolerance in diabetes mellitus 701
Gibson, T. E.: Diagnosis of adrenal tumors with classification of adrenal tumor syndromes.. 91
Gilligan, D. R.: cf. Gargle.....699
Gilman, P. K. (Kay): Certain advantages of total thyroidectomy in selected cases of thyrotoxicosis of the exophthalmic type 371
Giroud, A.: cf. Binet.....505
Glassberg, B. Y. (Somogyi and Taussig): Diabetes mellitus..113
Gley, P : Histological changes in female reproductive organs under the influence of the hormone of the corpus luteum...817
— Inhibition of ovulation by the corpus luteum 514
Gnoinski, H.: Effect of insulin on the blood-sugar in nephrectomized dogs 524
Goldberger, M. A.: cf. Frank...216
Golding, G. T. (Ramirez): Ovarian and placental hormone effects in normal, immature, albino rats 804
Gordon, A. H. (Connor and Rabinowitch): An unusual case of diabetes mellitus; death after thirteen years' observation; necropsy 222
Gordon, B.: cf. Cantarow.....118
Gordon, M. B.: Stammering produced by thyroid medication..534
— Childhood myxedema 706
Grant, S. B.: Management of goiter patients with congestive heart-failure 237
Greenberg, D. S.: cf. Nice.....692
Greenberg, S. L.: cf. Nice.....692
Greenwald, I.: Does feeding of cod-liver oil prevent tetany in thyroparathyroidectomized dogs? 829
— Do blood and serum contain some protective agency against the sequelae of parathyroidectomy? 367
Grier, G. W.: X-ray treatment of goiter 371

Grönberg, A.: Is cutis verticis gryata a symptom in an endocrine syndrome which has so far received little attention...110
Grote, I. W.: cf. Kramm..358, 699
Gruber, C. M.: XVIII. The depressor effect of epinephrin in decerebrated animals 507
Grueter, F.: Contribution to the study of function of the anterior lobe of the hypophysis 821
Guardabassi, M.: Initial hyperglucemic effect of insulin.....114
Guggenheim, M.: cf. Asher.....687
Guillaumie, M.: cf. Gayet..... .....211, 222, 524
Guttmacher, A. F.: cf. Wang...106
Gyorgy, E. (Mihalovics): Rôle of thymus in chloroform narcosis 232
Gyorgy, P.: cf. Grehme.....230

Habein, H. C.: cf. Snell.....533
Haberlandt, L.: A hormone of heart beat. VIII. Radiation experiments with fluorescent, ultraviolet, and Röntgen rays.357
— Hormone of the heart-beat...106
— Hormone of heart movement. IX. Experiments with heart-extract of warm-blooded animals 519
— New researches on the heart-hormone 211
Haines, S. F.: Exophthalmic goiter and myxedema 55
Haldeman, K. O.: Tumors of pineal gland 121
Hamburger, W. W. (Lev): Basal metabolism in organic heart disease 372
— (Lev, Priest and Howard): Studies on heart in thyroid disease. Changes in T'wave of the human electrocardiogram following iodin medication and thyroidectomy..371
Hammett, F. S.: A biometrical study of the size inter-relationship of the glands of internal secretion 353
— Interpretative generalizations from differential development observed in conditions of thyroid and parathyroid deficiency 124
— Rôle of thyroid and parathyroid in growth of heart and lungs 123
Hammett, F. S.: Rôle of thyroid apparatus in growth of liver, kidneys and spleen.....123
Hanisch, Sofie (Junkersdorf): Experiments on phloridzin. VII. Metabolism in phloridzin diabetes on an unbalanced protein diet 114
Hannan, John H.: Epinephrine sensitiveness at the menopause 59
— Observations on oral administration of oestrus producing autacoid 193
Hanson, A. M.: Standardization of parathyroid activity 367
Harbinson, J. E.: The conservative treatment of gangrene complicating diabetes 361
Harris, Katharine D. (Smith): Histological study of the thyroid of the guinea pig in experimental scurvy 534
Hart, P. C.: cf. Laquer....101, 515
Hartman, F. A. (Evans and Walker): Action of epinephrin upon capillaries and fibers of skeletal muscle 692
— (MacArthur and Hartman): Substance which prolongs life of adrenalectomized cats 91
Hartman, J.: cf. Abderhalden..122
Hartman, W. E.: cf. Hartman.. 91
Hawley, Estelle E.: cf. Murlin.115
Heath, C.: cf. Aub.....233
Hédon, E.: Is there a substance producing hyperglycemia in blood of diabetes?.....524
Hédon, L.: Basal metabolism in experimental pancreatic diabetes 524
Heideman, A. G.: cf. Womack..773
Herman, L.: cf. Canciulesco....505
Hermann, H.: cf. Tournade 510, 511
Hetenyi, G.: Mechanism of the action of synthalin 524
Higgins, G. M. (Sheard): Effects of selective solar irradiation on parathyroid glands 826
Hill, Elsie: cf. Blatherwick....522
Hines, H. M. (Leese and Jacobs): Effect of pituitrin administration upon distribution of injected fluid 110
Hirsch, H.: Cyclic variations of sex hormone content of blood in women 515
Hirsch, R.: cf. Canciulesco.....505

Hirst, J. C., II.: The clinical use of ovarian follicular hormone with special reference to functional sterility.....695
Hjort, Axel M.: Antidiuretic effect of pituitary exytocic and pressor principles on water diuresis in man 496
Hoff, H. (Wermer): Influence of diuretics on pituitrin secretion 357
Hohlweg, W.: cf. Steinach.....517
Holm, K.: Quantitative and optimal action of insulin.....361
Holsti, Ö.: Influence of potassium iodide and thyroid preparations upon blood sugar curve.....114
Hornung, S.: Results of prolonged treatment of normal animals with insulin 223
Horrax, G. (Bailey): Pineal pathology 368
Horrenberger, R.: Cytological studies on human corpus luteum 818
Hoskins, F. M. (Snyder): Calcium content of maternal and foetal blood serum following injection of parathyroid extract in foetuses in utero.....532
Hoskins, Margaret M.: Effect of acetyl thyroxin on teeth of new-born rats 238
Houssay, B. A. (Mazzocco): Glutathione and reducing properties of tissues of decapsulated rats 211
— Variations of glycogen in heart and brain, and of lactic acid and hexose phosphate in muscles in adrenalectomized rats 91
— (Molinelli): Output from adrenal anastomosed to blood vessels of neck 92
— — Vagus nerve and secretion of adrenin from adrenals.212
— — The effect of neurine and ephedrine on the secretion of adrenin.....508
Howard, H. C.: cf. Hamburger.371
Howell, W. H.: The purification of heparin and its chemical and physiological reactions...512
Hubener, H.: cf. Kurtzman....126
Huffman, J. W.: cf. Dragstedt.. .....506, 507, 691, 813
Hunt, H. Lyons: Technic of gland transplantations 491
Hutton, J. H.: Endocrine disorders related to more common syndromes 214
Hyams, J. A.: cf. Kwartin.....101
Hyman, H. T.: cf. Kessel.....239

Ishikawa, Y.: cf. Geiling.....113
— cf. Supniewski 118
Issekutz, B. V.: Contributions on the action of insulin.....361
Iwanow, G.: Embryology of the chromaffin system in man....352
— Topography of the paraganglia in man 352

Jacobovici, J. (Nitzescu and Pop): Function of carotoid body. Relation to carotid sinus reflex 694
Jacobs, H. R.: cf. Hines.....110
Jacobsohn, M.: cf. Rothschild..243
Jaffe, R. (Berberich and Fisher): Handbuch der inneren Sekretion (Book Review).....686
— (Tannenberg and Josephy): Handbuch der Inneren Sekretion 687
Jameson, H. L.: cf. Anders....223
Jaques, L.: Cataract and post-operative tetany 535
Jensen, H.: cf. De Vigneaud...523
John, H. J.: Study of 22,800 blood sugar estimations—fasting and postrandial—in non-diabetic individuals 525
Johnson, W. O.: Psychosis and hyperthyroidism 706
de Jongh, S. E.: cf. Laquer.101, 515
Jonsson, E. (Aderman): The size relations of the human adrenal during foetal life....508
Josephy, H.: cf. Jaffe (Book Review) 687
Joslin, E. P.: Ideals in the treatment of diabetes and methods for their realization 525
Joslin, H. F. (White): Diabetic coma and its treatment.....224
Joyce, T. M.: cf. Menne.....536
Jung, Frederic T.: Effects of ultra violet light on parathyroidectomized rats.....81, 829
Jung, L. (Auger): Insulin blood pressure and vagus tonus.....224
Junkersdorf, P.: cf. Hanisch...114
Jutchenko, V. I.: cf. Sharapov..700

Kahnt, Lydia C. and Edward A. Doisy: Vaginal smear and assay of ovarian hormone.....760
Kalnins, V.: Action of thyroxin on autonomic nervous system.535
— Effect of thyroxin on autonomic excitability of heart.535

Kamm, O. (Aldrich, Grote, Rowe and Bugbee): The active principles of the posterior lobe of the pituitary gland. I. The demonstration of two active principles. II. The separation of the two principles and their concentration in the form of potent solid preparations. 358, 699
— cf. Bugbee 671
Kampmeier, R. H.: cf. Youmans. 376
Kay, W. E.: cf. Gilman.....371
Kellar, T.: cf. Bencan.....514
Keller, T.: cf. Champy.....355
Kelly, T. H. (Whippern): Injuries to the recurrent laryngeal nerve in operations of the thyroid gland 238
Kendall, E. C.: Seasonal and geographic variations in the iodine and thyroxin content of the thyroid 830
Kepinov, L. (Dutaillis): Changes in glycemia seen in depancreatized dogs which carry pancreatic grafts following operation and ingestion of glucose..824
— (Petit-Dutaillis): Glucose as physiological excitant of internal secretion of pancreas 225
— — The hyperglycemic effect of blood from depancreatized dogs 525
Kern, Ruth: cf. Buchbinder....532
Kern, R.: cf. Kunde.....832
Kerr, W. J.: Geographical distribution of goiter 238
Kessel, L. (Hyman): Exophthalmic goiter and involuntary nervous system. Influence of subtotal thyroidectomy with and without compound solution of iodine on course of disease 239
Kibjakow, A. W.: cf. Putschkow 353
King, Jessie L.: Activity and working power of uterine muscle of non-pregnant sow.....100
Klein, H.: Striopallidal and bulbar symptoms in exophthalmic goiter.....372
Knudson, A.: cf. Randles.....353
Kotschneff, Nina: Sugar content of whole blood of different vessels and its partition between plasma and corpuscles under normal conditions and after insulin and adrenine administration to angiostomized dogs.525
Kountz, W. B.: cf. Loeb.....696
Kraft, R.: The influence of the thyroid on the distribution of iodine, sugar and amino acids in the blood 535
Kramer, D. W.: Hypertension and diabetes 701
Krantz, C. I. (Means): Effect of epinephrin on partition of food stuffs in obese and normal individuals 92
Krinizki, J. M.: Treatment of tetany and spasmophilia in adults by bone transplantation 367
Križenecky, J.: Observations on antagonism between thyroid and thymus in controlling body weight 831
— (Nevalonnyj): Further experiments on the influence of the thyroid and the thymus on feather development in poultry 831
— (Nevalonnyj and Petrov): Experiments on function of thyroid and thymus in the regeneration of plucked feathers 832
— (Podhradsky): Concerning influence of hyperthyroidism on the maturation, growth and pigmentation of the feathers in full-grown fowls 831
Kun, H.: cf. Steinach.....517
Kunde, Margaret M.: Experimental hyperthyroidism 124
— (Carlson): Experimental cretinism. I. A rachitic-like disturbance in extreme hypothyroidism 126
— (Williams): Experimental cretinism. II. Influence of thyroid glands on production and control of experimental rickets 126
— (Oslund and Kern): Prevention of fatal parathyroid tetany in thyroparathyroidectomized dogs, by administration of thyroid hormone 832
Kurtzman, H. (Hubener): Thyroid gland substance implantations 126
Kwartin, B. (Hyams): True hermaphroditism in man.....101

La Barre, J.: Answer to Gayet and Guillaumie on the regulation of the internal secretion of the pancreas 824

La Barre, J.: Does nervous system influence the supply of insulin under normal condition?.225
— Increased insulin output following injection of posterior hypophysis extract 225
— On the increase in insulin following injection of posterior lobe extract 526
— cf. Zunz.....229, 367, 825
Labbé, M. (Roubeau, Nepveux): Action of nickel and cobalt salts on the hypoglaucaemic power of insulin on the diabetic 362
— — Influence of nickel and cobalt on the hypoglycaemic action of insulin on the rabbit.....362
Lackey, R. W.: cf. Reed.....231
Lahm, W.: cf. Aschner.....688
Lange, F.: cf. Loewe.....356
Langfeldt, Gabriel: The endocrine glands and autonomic systems in dementia praecox (Book Review) 349
Laquer, E.: Concerning female sex hormone, Menformon 515
— (Hart and de Jongh): The female sexual hormone, Menformone. VII. The action of the ovarian hormone, especially Menformone, administered by mouth, and the importance of its administration in several doses.....515
Laqueur, E. (Hart and de Jongh): Note on preparation and properties of female sex hormone (Menformon) in water-soluble form 101
— (de Jongh and Tausk): The feminizing influence of the female sex hormone (menformon) on the undeveloped mammary gland 101
Larson, E. (Elkourie): Tissue changes in parathyroid tetany and in guanidine poisoning...826
— — Rôle of toxins in parathyroid tetany. I. An attempt to control tetany by oral administration of kaolin 119
— (Fisher): Effects of thymus muscle and pituitary extracts on normal and thyroparathyroidectomized dogs.519
— cf. Fisher 335
Latta, Ruth E.: cf. Murlin....702
Lawrence, Charles Henry (Rowe): Studies of the endocrine glands. III. The thyroid 377
Lawrence, C. H.: cf. Rowe.....1, 245, 591, 707
Lawrence, R. D.: Relationship between body temperature and blood sugar in rabbits 225
Leake, C. D.: Effects of prolonged administration of desiccated spleen and red bone marrow on the blood-forming centers of rabbits 122
Lee, F. C.: cf. Lewis.....519
Lee, M. O. (Van Buskirk): Studies on vigor. XV. The effect of thyroidectomy on spontaneous activity in the rat, with a consideration of the relations of the basal metabolism to spontaneous activity 536
Lee, R. I.: Thyroid dysfunction as cause of fever.....240
Leese, C. E.: cf. Hines.....110
Le Fevre, W. M.: Evidence concerning the effect of insulin on carbohydrate tolerance 526
Léhman, E. P. (Cole): Parathyroid hormone and calcification of fracture callus.....121
Leifer, A.: Case of insulin edema 362
Leitch, D. B.: Use of parathormone in the treatment of infantile tetany 368
Lesure, A.: cf. Loeper.....813
Lev, M. W.: cf. Hamburger.371-372
Levy: cf. Nobecourt.....364
Lewis, D. (Lee): Glandular elements in the posterior lobe of the human hypophysis 519
Lipschutz, A.: Hermaphroditism in pressure of intact testis....216
— Peculiar type of intersexuality in guinea-pig 101
— (Vinals): Impregnation by a guinea pig rendered hermaphroditic 216
Lisser, H.: cf. Atkinson.....680
Loeb, L.: On the graded relation between the intensity of hormone action and the character of the recipient tissue...161
— The effects of hysterectomy on the system of sex organs and on the periodicity of the sexual cycle in the guinea pig 356

Loeb, L. (Kountz): The effect of injection of follicular extract on the sex organs of the guinea pig and the interaction between the follicular substances and substances given off by the corpus luteum.....696
Loeper, M. (De Court and Lesure): Accumulation of sulphur in the skin after adrenalectomy 813
Loewe, S. (Lange): On ovarian hormone 356
— cf. Voss 521
Lohmann, Anne: cf. Berglund..367
Longcope, W. T.: Hypoglycemia in scleroderma 352
Lurie, Mark: Storage of sulphur in adrenal glands..... 84
Lutz, B. R. (Wyman): The chromaphil tissue and the interrenal bodies of Elasmobranchs and the occurrence of adrenin 508

MacArthur, C. G.: cf. Hartman. 91
Macdonald, A. D. (Schlapp): Adrenaline vaso-motor dilation 508
Macdonnel, P. M.: cf. Miller...537
Macht, D. I. (Stickel and Seckinger): Effect of lutein injections on oestrous cycle of the guinea pig 818
MacKay, E. M. (MacKay): Enlargement of the adrenal cortex in experimental uremia.....509
MacKay, L. L.: cf. MacKay....509
Magenta, M. A.: Action of the salts of nickel and cobalt on insulin hyperglycemia 526
Majanz, A. J.: cf. Fertik.....512
Marañon, G.: El bocio y el cretinismo (Book Review).....688
— Induced blood sugar curve found in muscular atrophy.363
— Spontaneous decrease of goiter in Spain 242
— (Sarda): Acid base equilibrium in Addison's disease..363
Marsh, H. E.: Suprarenal insufficiency: Report of two cases.692
Martin, K. A.: Conditions under which iodin will cause a change in the basal metabolic rate in man. I. Its occurrence in conditions other than that of Graves' disease 373
Marx, H.: Regulations of the blood sugar and water concentrations 526
Marza, V.: cf. Parhon.....214
Mason, E. H.: Case of diabetes mellitus that became one of atypical glycosuria 527
— Occurrence of a raised basal metabolic rate in new growth without hyperthyroidism 536
— (Flack): A case of chronic glycosuria, probably of extra pancreatic etiology 363
Masterman-Wood, J. L.: Adiposity of pituitary and thyropituitary origin in adult; diagnosis and treatment 127
Matthews, S. A.: cf. Austin....119
Mauriac, P. (Aubertin): The insulin neutralizing power of the blood of diabetics and nondiabetics 527
Mazzocco, P.: cf. Houssay..91, 211
McCarrison, R.: Experimental productions of new type of goiter unrelated in its origin to iodine 241
— (Newcomb, Viswanath and Norris): Relation of endemic goiter to the iodine content of soil and drinking water 240
McClenahan, W. U.: cf. Norris.824
McLean, A. J.: Route of absorption of pituitary secretion....467
McNinch, J. H.: cf. Durant....813
Means, J. H.: cf. Krantz..... 92
Medes, Grace: cf. Berglund....367
Menne, F. R. (Joyce and Stewart): Clinical and pathological evidence of the influence of iodine in the therapy of primary hyperthyroidism 536
Menninger, W. C.: Oral administration of epinephrine.....212
Mermod, Camille: cf. Engle...821
Messerle, N.: State of blood sugar and adrenalin skin reactions after quartz-mercury vapor lamp irradiation and after sun baths 226
Mestrezat, W. (Caulaert): The presence of pituitrin in the ventricular cerebro-spinal fluid and its absence in the lumbar cerebro-spinal fluid.....520
Mihalovics, G.: cf. Gyorgy.....232
Miley, H. H.: cf. Gans..... 91
Miller, J. (Macdonnell and Cadenhead): Case of exophthalmic goiter complicated with toxic adenoma treated by lead ionization 537

Mills, C. A.: Diabetes among the Chinese. Danger of insulin usage 364
— Treatment of diabetes with an acid-alcoholic extract of plants rich in vitamin B...528
de Mira, T., jun.: Suprarenal tissue in the food of mice. Effect on the development of the organism and on the sexual function 509
de Mira, F. (Fontes): Muscular fatigue in decapsulated rabbits.814
Mirvish, L. (Bossman): Influence of the internal secretion of the ovary on the calcium blood level and on calcium metabolism 515
Mix, C. L.: Exophthalmic goiter of peculiar type 242
Molinelli, E. A.: cf. Houssay.. .....92, 212, 508
Monossohn, S. M.: cf. Fertik...512
Moore, R. A.: A case of diabetes, refractory to insulin with hyperplastic and adenomatous adrenals 800
Morgulis, S. (Schatzilio): Influence of internal secretions and of trephones on phagocytosis..832
Mori, K.: Influence of thyroid and insulin on the oxidases of the various organs.....537
Morrison, L. B. (Bogan): Bone development in diabetic children 115
Mosser, W. B.: cf. Frazier.....370
Mouzon, J.: What should one think of the "heart hormone"?.819
Moya, A.: cf. Bonilla.....351
Murase, H. (Nakajima): Action of adrenaline and carcium on heart 92
Murlin, J. R. (Latta): Absorption of insulin from Thiry vella fistulae in normal and depancreatized dogs 702
— (Hawley): Absorption of insulin from alimentary tract of pancreatized dogs, when protected by blood serum..115
Murphy, F. D.: cf. Thalhimer..825
Murray, W. S.: Ovarian secretion and tumor incidence....102

Nadler, W. H.: cf. Elliott.....221
Nakajima, K.: cf. Murase..... 92
Nelson, E. E.: Antagonism between quinine or quinidine and epinephrin 93
Nepveux, F.: cf. Labbe.....362
Nevalonnyj, M.: Effect of hyperthyroidism on the development of intersexual forms in chickens 373
— cf. Križenecky 831-832
Newcomb, C.: cf. McCarrison..240
Newton, H. F.: cf. Zwemer....693
Nice, L. B. (Greenberg and Greenberg): Rat activity and adrenalin 692
Nikolaeff, M. P.: Experiments on isolated ovaries.....696
Nitzescu, I. I. (Gavrila): Rapidity of sedimentation of red blood cells in human diabetes.364
— (Marie Benetato): Hypophysis and glycogenesis.....359
— (Ramneantu): Note on mechanism of pituitary hyperglycemia 218
— cf. Jacobovici 694
Nobecourt (Levy): Injection of insulin and thyroid in large doses in cachexia of nurslings.364
Nonnenbruch, W.: Metabolic tests in dystrophia adiposo-genitalis.520
Norris, G. W. (McClenahan) Hypertrophy (adenoma?) of the islands of Langerhans with associated hypoglycemia.....824
Norris, R.: cf. McCarrison.....240
Nóvoa Santos, R.: Effect of duodenal secretin upon the secretion of insulin by pancreas...199

Ohara, Y.: The effects of successive doses of insulin on the animal body 527
Okuda, M.: Adrenalin content of suprarenal capsule in chick embryo 342
Olesen, R.: Endemic goiter in Oregon 373
Oliveira, J. C.: cf. Coelho.....523
Orator, V.: Exophthalmic goiter and diabetes 127
— (Walchshoper): Adolescent thyroid and goiter in Steirmark 243
Orlandi, N.: Peduncle of the human hypophysis 218
Ortega, F. E.: Parathyroid extract as a factor in ossification and growth 533
Oslund, R. M.: Experiments with follicular and placental extracts 819
Oslund, R.: cf. Kunde.....832
Otto, H. L.: Action of epinephrin upon cardiac rhythms..... 93

Pacher, H.: cf. Von Fellenberg.128
Padgett, E. C. (Orr): Insulin-glucose treatment of traumatic shock 528
Pak, C.: Oxytocic power of pituitary under different circumstances 219
Palmer, W. W.: Effect of iodine on creatinuria in hyperthyroidism 374
Parhon, C. I. (Cahane and Marza): Changes in water content of liver as influenced by some internal secretions 214
Parkes, A. S.: Occurrence of oestrus cycle after x-ray sterilization. Irridation of the adult during pregnancy and lactation 102
— Occurrence of oestrus cycle after x-ray sterilization. Periodicity of oestrous after sterilization of adult.....217
— (Bellerby): Studies on internal secretion of ovary. V. Oestrus - inhibiting function of corpus luteum.....516
— (Brambell): The causation of the anoestrous period.....516
Parsons, Eloise (Randall and Wilder): Pregnancy and diabetes 226
Patterson, T. L.: The influence of prostatectomy on the sex life of the male albino rat....697
Pautrier, L. M. (Ullmo): Large ulcers of the leg of fourteen years' duration healed within twenty days with insulin pommade 702
Payte, J. I.: cf. Reed.....231
Peabody, F. W.: Report of case of diabetes insipidus.....219
Perelmutter, Z. M.: cf. Zawadovsky 128
Permar, H. H.: cf. Wedd.....834
Peruche, de Paula: Action of adrenin in asthma and hay fever 212
Peserico, E.: Action of insulin on respiratory metabolism of isolated mammalian heart ...115
Petit-Dutaillis, S.: cf. Képinov 225, 525
Petty, O. H.: Diabetes and its treatment by insulin and diet. A hand book for the patient. Book Review 688
— (Stoner): Respiratory quotient curves in diagnosis in diabetes 116
Petrillo, L. M.: cf. Rosello....797
Petrov, I.: cf. Križenecky.....832
Pezard, A.: Experimental basis for theory of sex differentials.103
Philpott, N. W.: Addison's disease in association with amyloidosis 509
Piazza, G.: Variations of phosphorus content in muscular tissue during insulin hypoglycemia 116
Plumier-Clermont (Garot): Hypertensive action of adrenalin following various routes of administration 212
Podhradsky, J.: cf. Križenecky.831
Ponticaccia, L. (Campanacci): Insulin therapy in carcinoma...116
Poos, F.: Physiology and pathology of pituitary.....822
Pop, A.: cf. Jacobovici.....694
Portmann, U. V.: Radiation therapy in malignant diseases of thyroid gland 127
Pototzky, C.: cf. Doxiades.....236
Potter, W.: cf. Stoland.....704
Pouget, E.: cf. Courrier.....514
Preston, Mary I.: Effects of thyroxin injections on suprarenals of mouse 323
Priest, W. S.: Case of hyperthyroidism simulating primary heart disease 242
— cf. Hamburger 371
Putnam, T. J. (Benedict): Further report of a case of experimental canine gigantism.....822
Putschkow, N. M. (Kibjakow): Toxic substances of the blood after extirpation of the adrenals 353

Rabinowitch, I. M.: Atrophy of subcutaneous fat following insulin injections 528
— Insulin and the mortality rate from diabetes mellitus.....365
— Observations on use of synthalin in treatment of diabetes mellitus 116
— cf. Gordon 222
Ramirez, F. T.: cf. Golding...804
Ramneantu, P. (Nitzescu).....218
Randall, L. W.: cf. Parsons....226
Randles, F. S. (Knudson): Studies on cholesterol. III. Relation of suprarenal gland and spleen to cholesterol metabolism 352
Rasmussen, A. T.: Morphology of pars intermedia of human hypophysis 129

Raspopwa, N. A.: cf. Zawadovsky 128
Reed, C. I.: Interrelations of calcium, phosphorus and sugar in parathyroidectomized dogs....827
— (Lackey and Payte): Relation of calcium and phosphorus in blood of parathyroidectomized dogs 231
Reichert, T. L.: The results of replacement therapy in an hypophysectomized puppy.....451
Reinhoff, W. F.: Hyperthyroidism and its relation to benign tumors of the thyroid gland..242
Rentz, E.: Action of insulin on experimental anaemia in the rabbit. Notes on inhibitory substances in blood during hyperglycemia 528
Retterer, E.: Monkey testicle grafts in man.....103
Richards, A. N.: cf. Dale.....210
Riddle, O.: The cyclical growth of the vesicula seminalis in birds is hormone controlled..516
— (Burns): Blood fat and phosphorus in sexes and their variations in reproductive cycle 104
— (Flemion): Sex difference in intestinal length and its relation to pituitary size....203
Robuschi, L.: cf. Enriquez..... 98
Rochlin, D. G.: Pseudoepiphyses in endocrinology 355
Rogoff, J. M. (Dominguez): Blood pressure following adrenalectomy 93
— (Stewart): Adrenal insufficiency: The beneficial influence of cortical adrenal extracts in adrenalectomized animals 693
— — Influence of "heat" on survival period of dogs after adrenalectomy 814
— — Studies on adrenal insufficiency. IV. The influence of intravenous injections of Ringer's solution upon survival period in adrenalectomized dogs.....510
— — Studies on adrenal insufficiency. V. The influence of adrenal extracts on the survival period of adrenalectomized dogs.....510
Rogoff, J. M. (Stewart): Studies on adrenal insufficiency. VII. Further blood studies (cholestrol and calcium) in control adrenalectomized dogs 814
Ropes, M.: cf. Aub.....233
Rosenberg, M.: Insulin thyroid antagonism 226
Rosenblatt, M. S.: cf. Cooksey..828
Rosello, H.: Relation of light to action of parathyroid extract.797
Rossides, T. N.: cf. Sollman... 94
Rothschild, F. (Jacobsohn): Action of ergotomine on the blood in Basedow's disease and in animals 243
Roubeau, H.: cf. Labbé.....362
Rowe, A. W.: Studies of endocrine gland. I. General method of diagnosis: abnormal functions 1
— Sugar tolerance as an aid to diagnosis 117
— (Lawrence): Studies of the endocrine glands. II. The pituitary 245
— — Studies of the endocrine glands. IV. The male and female gonads.....591
— — Studies of the endocrine glands. VI. The pluriglandular syndromes....707
— cf. Lawrence 377
Rowe, L. W.: Studies on oxytocin and vasopressin: effect on melanophores 663
— cf. Kamm 699
— cf. Kramm 358
Rubens, O.: Thyroid gland in young adults 374
Ruedemann, A. D.: Ocular disturbances in diabetes.....227

Sahyun, M.: cf. Blatherwick...111
Saida, M.: Acid base equilibrium in thyroid disease.....375
Saito, S.: Effect of hemorrhage upon rate of liberation of epinephrine from suprarenal gland of dogs 693
Sakurai, T.: Lowering of blood sugar through parasympathetic stimulation 365
Sammartino, U.: Further contribution to study of action of insulin on the ferments.....117
Sandiford, I.: cf. Boothby.....234
Sandiford, K.: cf. Boothby....234
Sansum, W. D.: cf. Blatherwick.522
Sarda, M.: cf. Marañon.....363

Sawitsch, W. W. (Speranskaja-Stepanowa): Influence of adrenin on vagus pulse..... 94
Schatzillo, B. A.: cf. Morgulis..832
Schenk, F.: Changes in the hypophysis of the rat during pregnancy 359
Schermann, S. J.: Effect of adrenaline on isolated heart after thyroidectomy 815
Schittenhelm, A. (Eisler): Effect of thyroxin in disorders related to the glands of internal secretion 375
Schlapp, W.: cf. Macdonald....508
Schoeller, W. (Gehrke): Action of thyroxin 537
— cf. Steinach 517
Schotté, O.: Rôle of pars intermedia in regeneration of batracians urodeles 111
Seager, L. D.: cf. Burge.....157
— cf. Wickwire 834
Searls, H. H.: cf. Terry.....120
Seckinger, D.: cf. Macht.....818
Selle, W. A.: Effect of glucose on ketosis 365
Sembrat, K.: Influence of thyroid gland of selacians and teleosts on the metamorphosis of frog tadpoles 243
Sendrail, M.: cf. Bernardbeig..533
Sevringhaus, E. L.: Difficulties in diagnosis of insulin coma..702
Sharapov, B. I. (Jutchenko): Roentgen-ray treatment of pituitary tumors 700
Sheard, C.: cf. Higgins.....826
Shen, T. C.: Creatinuria and castration 357
Shepardson, H. Clare: cf. Atkinson 680
Shields, W.: cf. Stansfield.....529
Shipner, L. B.: The action of myrtillin in pancreatic insufficiency 528
Shohl, A. T. (Wakeman and Shorr): Effect of parathyroid extract on mineral metabolism in infantile tetany.....533
Shorr, E. Y.: cf. Shohl.....533
Simola, P. E.: Insulin-like substances in higher plants and micro-organisms 529
— The action of synthalin on the organism 529
Simon, F.: Blood-sugar content and insulin treatment of dermatoses 117
Simond, A. E.: cf. Bugbee.....698
Simonnet, H. (Tanret): Hypoglucaemic properties of galegine sulphate 365
— cf. Brouha 99, 215
Simonnet, S.: The study of the internal secretion of the ovary. The properties of the follicular liquid. I. Concentration, properties of the folliculine.....516
Slosse, J.: cf. Boothby.....234
Smith, Erma A.: cf. Harris....534
Smith, E. E.: cf. Wakefield.... 96
Smith, J. F.: cf. Gardiner-Hill.370
Smith, J. H.: Basal metabolism. III. Influence of work with special reference to thyroid gland 833
Smith, L. W. (Clute and Striedler): Results of one hundred consecutive cases of hyperthyroidism operated upon. A clinical and histological study attempting to correlate the morphology and clinical picture, with a view to prognosis.....375
— cf. Crosbie 506
Smith, M. G.: Ovarian follicular hormone in blood of pregnant women 104
Smith, M. I.: cf. Sullivan.....823
Smith, W. E.: cf. DeQuervain..177
Snell, A. M. (Habein): Tetany and chronic diarrhea.....533
Snyder, F. F.: Presence of melanophore-expanding and uterus-stimulating substance in the pituitary body of early pig embryos 822
— cf. Hoskins 532
Soler, B.: Glycemic curve in states of prediabetes.....366
Sollman, T. (Rossides): Effects of epinephrine on auricular tonus waves of turtle heart.... 94
Somogyi, M.: cf. Glassberg....113
Soskin, S.: On the "Calorigenic Action" of epinephrin..... 94
Speranskaja-Stepanowa, E. N.: cf. Sawitsch 94
Spohn, H.: Enlarged thymus. Some observations on the physiology and anatomy of the thymus and thyroid glands...232
Stanley, P.: cf. Swingle.....368
Stansfield, O. H. (Shields): Inflammation involving islands of Langerhans in diabetes.....529
Starr, P.: cf. Elliott.....221
Stasiak, A.: Inactivity of insulin injected directly into intestine and experiments to ascertain cause of inactivity 530

Steinach, E. (Dohrn, Schoeller, Hohlweg and Faure): Biological action of female sex-hormone 517
— (Kun): The importance of the pituitary in the mechanism of development as activator of gonadal secretion 517
Steinen, R. v. d.: Fate and characteristics of Mongolian children 244
Stern, F.: cf. Altenberger.....820
Stettiner, H.: Steinach operation 357
Stewart, G. N.: cf. Rogoff..... 510, 693, 814
Stewart, J. D.: cf. Menne.....536
Stickel, A.: cf. Macht.....818
Stoland, O. O. (Potter): Vagocardiac irritability following guanidine intoxication and in parathyroid tetany 704
Stone, C. P.: cf. Doe-Kulmann. 98
Stoner, W. H.: cf. Petty.....116
Striedler, J. W.: cf. Smith.....375
Strisower, R.: Insulin and blood pressure 530
Strouse, S. (Daly): Diabetes and pregnancy 227
Sturr, R. P.: Early diagnosis and treatment in enlargement of the thymus gland.....233
Sugawara, T. (Tada): Effect of guanidine hydrochloride upon the epinephrine output from the suprarenal gland and sugar content of blood in dogs..... 94
Sullivan, M. X. (Smith): Loosely-bound sulfur in pituitary extracts 823
Supniewski, J. V. (Ishikawa and Geiling): Effect of insulin injected into cerebrospinal fluid.118
Susani, O.: Relationship of endemic goiter to tuberculosis..244
Susman, W.: Insulin and the diabetic pancreas 530
Swingle, W. W. (Wenner): Sulfate retention in dogs following bilateral adrenal extirpation 353
— (Wenner and Stanley): Effect of CO_2 administration upon parathyroid tetany...368
Szent-Györgyi, A. V.: Functions of adrenal cortex and mechanism of biological oxidations... 95

Tada, H.: cf. Sugawara..... 94
Takashima, T.: Three cases of thymus death of infants.....122
de Takats, G.: Indications for thyroidectomy 244
Tamura, Y.: Structural changes in suprarenal gland of mouse during pregnancy..... 95
Tannenberg, I.: cf. Jaffe. Book Review 687
Tanret, G.: cf. Simonnet.....365
Tausk, M.: cf. Laqueur.....101
Taussig, A. E.: cf. Glassberg..113
Terry, W. I. (Searls): Parathyroid preservation 120
Thalheimer, W. (Murphy): Carcinoma of islands of pancreas.825
Thayer, Sidney (Doisy): Distribution of hormone in ovary...769
Thivolle, L.: cf. Fontes.....701
Thomas, E.: Innere Sekretion in der ersten Lebenszeit.....690
Thomas, H. M.: Nodular goiter with hyperthyroidism 537
Titajev, A. A.: cf. Zawadovsky.128
Topper, A. (Cohen): Effect of thyroid therapy on children...833
Torrey, Harry B.: Thyroxin as depressant of cell division; its effect on cleavage and early development of sea urchin and ascidian 65
Tournade, A.: Does adrenin exert a stimulating action on vaso-motor centers? 213
— (Hermann): Adrenin output in peptone shock.....511
— — Chloralose and the secretion of adrenin.....510
Toverud, K. U.: Insulin and treatment of juvenile diabetes mellitus 227
Trichera, C.: importance of site of attachment of testicular transplants 819
Truffi, G.: Follicular liquid and ovarian hormone 518
— Ovarian hormone 105
Tuisk, R.: Protracted oestrus induced by ovarian extracts....105

Ullmo, Mlle.: cf. Pautrier.....702
Umber, F.: Use of synthalin in diabetes 118

Van Buskirk, E. F.: cf. Lee....536
Van de Scheer, W. M.: Mongolian maldevelopment, upon the basis of clinical, statistical and anatomical investigations.....243
Van Dyke, H. B.: Iodine compounds. Their selective absorption by the hyperplastic thyroid gland in the dog.....834

Velasco, J. F.: cf. Bonilla.....534
Velardi, F.: Adrenals and solar plexus in anaphylaxis..... 96
Veler, C. D. (Doisy): Extraction of ovarian hormone from urine.697
Viale, G.: The cholin forming properties of the adrenals....511
— The supposed antitoxic action of the adrenals.....511
Vichnjitch, M.: cf. Chahovitch 506, 695
du Vigneaud, V.: Is insulin inactivated by glucose?.....366
— Sulphur of insulin.....366
Vignes, H.: Treatment of habitual abortions by thyroid extract 376
Viswanath, B.: cf. McCarrison..240
Vogt, E.: Relationship between insulin and ovaries and its therapeutic value in treatment of uterine hemorrhage.....105
Von Fellenberg, T. (Pacher): Iodine content of thyroid gland of various types of cattle and its relation to glandular condition 128
Voss, H. E. (Loewe): Sex-determining action of anterior pituitary on males.....521
van Wagenan, Gertrude: Growth response to anterior hypophyseal extract by the castrated male rat 521

Wagenseil, F.: Consequences of castration and of eunuchoidism in man 697
Waggener, R. A.: cf. Dye.....828
Wakeman, A. M.: cf. Shohl....533
Wakefield, E. G. (Smith): Addison's disease, suprarenalopathies, sclerosis of the glands of internal secretion 96
Walchshoper, E.: cf. Orator...243
Walker, Helen G.: cf. Hartman.692
Wang, G. H. (Guttmacher): Effect of ovarian traumatization on spontaneous activity and genital tract of albino rat, correlated with histological study of ovaries 106
Wastl, Helene: Influence of adrenalin and of some other internal secretions on contractions of skeletal muscle of warm-blooded animals 511
Watanabe, M.: Simultaneous determination of the blood sugar content and the epinephrin output from the suprarenal gland in non-anaesthetized, non-fastened dog during peptone poisoning 96
Weber, J. J.: cf. Chaikoff.360, 522
Wedd, A. M. (Permar): Ophthalmoplegia in Graves' disease 834
Weiss, T.: Diabetic coma and insulin 531
Wenner, W. F.: cf. Swingle.353, 368
Wermer, P.: cf. Hoff.....357
Wertheimer, E.: Regulation of metabolism. X. Glycogen in fatty tissue and possibility of change in fat into carbohydrate 531
— cf. Abderhalden 122
White, A. C.: Effect of adrenalin on intestinal volume.....213
White, Priscilla: cf. Joslin....224
Wickwire, G. C. (Seager and Burge): Proof that desiccated thyroid increases sugar utilization, while commercially prepared thyroxin and other iodine compounds do not.....834
— cf. Burge 157, 700
Wiechmann, E.: Permeability of peripheral tissues for dextrose in epinephrin diabetes.....228
Wightman, A. H.: cf. Dragstedt 210, 507
Wilder, P. M.: Hyperthyroidism, myxedema and diabetes.....228
— cf. Parsons 226
Williams, L. A.: cf. Kunde....126
Wintersteiner, O.: cf. De Vigneaud 523
Wishnofsky, M.: Studies in calcium and carbohydrate metabolism. I. Calcium and glucose tolerance in diabetes mellitus.229
Wollstein, Martha: Neuroblastoma of the adrenal in young children 511
Womack, N. A. (Cole and Heideman): The thyroid gland in infections; the effect upon the basal metabolic rate.....773
— cf. Cole 369
Worster-Drought, C. (Dickson and Archer): Dyspituitarism of the Lorain type, associated with a pituitary cyst arising from Rathe's cleft and secondary lesions in the hypothalamic region and ventricles.....359

Wyman, L. C.: Effect of suprarenal insufficiency on the oestrous cycle in the albino rat..816
— Effect of thyroidectomy and of forcing fluid on susceptibility to toxins in suprarenalectomized rats 815
— cf. Lutz 508

Yater, W. M.: Acromegaly and diabetes 703
Yohoh, A.: Extirpation of pineal gland and gonads.....231
Youmans, J. B. (Kampmeier): Effect of iodine in toxic adenoma 376

Zacherl, H.: Oestrus periods of rats in parabiosis.....357
Zawadovsky, B. (Titajio, Perelmutter and Raspopowa): Action of iodine preparations on metamorphosis of axalotls....128
Zimmerman, L. M.: Effect of parathyroid hormone on blood coagulability 119
Zondek, B. (Aschheim): Ovum and hormones 217
— cf. Ascheim 513
Zung, E. (La Barre): Cause of hyperinsulinemia in the pancreatic vein following dextrose hyperglycemia 229
— — Cause of increase of insulin in the following intravenous injection of synthaline 367
— — Direct stimulation of islands of Langerhans by adrenin 825
Zwemer, R. L. (Newton): Asphyxial stimulation of the denervated adrenal gland.....693

Subjects

Acromegaly 245
— and diabetes 703
— studies in 108
Action of adrenin on activity of fatigued muscle in decapsulated rabbits 814
Addison's disease and amyloidosis 509
— — — blood sedimentation ...351
— — — diabetes mellitus occurring simultaneously.. 89
— — — insulin 363
— — — sclerosis of glands of internal secretion 96
— — report of two cases.....692
Adiposity and diabetes mellitus.223
Adolescent thyroid and goiter...243
Adrenal, see also suprarenal.
— ablation and blood pressure..691
— — — — studies 814
— — — cholesterol content of blood 353
— — — choline 353
— — — infection 351
— — — influence of heat on survival period 814
— — — injections of Ringer's solution 510
— — — sulphur in skin.....813
— — blood pressure following.. 93
— — ergographic studies after.. 91
— — substance which prolongs life after 91
— — variations of lactic acid and hexose phosphate in muscle after 91
— anatomy, embryology, morphology of 687
— and cholin formation 511
— — insulin 527
— — metabolism 1
— — muscular action 814
— — sedimentation velocity of red corpuscles 97
— — solar plexus in anaphylaxis 96
— — temperature control 506
— — x-ray 335
— cortex, action of, on growth.. 90
— — enlargement of, in experimental uremia 509
— — functions of 95
— cortico-medullary relations of.506
— denervation and asphyxial stimulation 693
— dysfunction and sugar tolerance test 117
Adrenal, effects of thyroxin on; compensatory hypertrophy in.323
— extirpation and sulfate retention 353
— — survival period of pregnant and lactating cat following 351
— extract and functional status of stomach 209
— — — intestinal volume.....213
— — — muscle circulation.....211
— — — vaso-motor centers.....213
— — hypertensive action of....212
— — in asthma and hay fever..212
— — vaso-dilator action of.....210
— gland and pregnancy 506
— — storage of sulphur in..... 84
— glutathione content 505
— histology of, in mouse; changes of, with age.....323
— hyperglycemia and sugar content of blood 525
— insufficiency 692
— — and adrenal extracts.....693
— — — oestrous cycle 816
— — — survival period 510
— lesions in symtomatic depressive syndromes 90
— neuroblastoma of in children.511
— tumors, diagnosis and classification of 91
— secretion and vagus.....212
— size relations in foetus.....508
— structural changes in, during pregnancy 95
Adrenin, anastomosed to blood vessels of neck..... 92
— action in fever..... 90
— and blood sugar.....225
— — — — skin baths after irradiation 226
— — carcium, action of, on the heart 93
— — islands of Langerhans....825
— — latent malaria 505
— — muscle contraction 511
— — — tonus 352
— — rat activity 692
— — sodium salt of barbital....209
— — vaso-motor dilation 508
— — — responses in unanesthetized dog 813
— — water content of liver....214
— blood sugar and sympathetic nervous system 89

Adrenin content of suprarenal capsule in chick embryo...342
— effect of injections of, on gastrocnemius 507
— — — on sugar metabolism...157
— — — — isolated heart after thyroidectomy 815
— influence of, on vagus pulse.. 94
— insulin antagonism 361
— method of biological assay of.690
— occurrence of, and chromaphil tissue and interrenal in Elasmobranchs 508
— secretion in peptone shock...511
— — and choloralose 510
— — — neurine and ephedrine..508
Adrenalectomy and carbohydrate metabolism 209
— reducing properties of tissues after 211
Amyloidosis and Addison's disease 509
Anoestrous, causation of.....516
Autonomic systems in dementia praecox 349

Basal metabolism 833
— — and the thyroid in infections 773
— — — heart disease 372
— — — hypophyseal tumor.....520
— — — iodin 373
— — — melano-sarcoma with liver involvement....536
— — — pancreatic diabetes.....524
— — — spontaneous activity...536
— — in endocrinopathies..... 1
— — — thyroid disease.....377
Basedow's disease and ergotoomine 243
Blindness and pituitary dysfunction 245
Blood and gonads.....591
— calcium and sunlight.....797
— chemistry in endocrinopathies 1
— fat and phosphorous, variations of, in reproductive cycle 104
— in thyroid disease.....377
— morphology in endocrinopathies 1
— pressure and pituitary dysfunction 245
— — following adrenal ablation 93
— — insulin and vagus tonus...224
— — of adrenalectomized rats..691
— sugar, adrenaline and sympathetic nervous system..... 89
— — and adrenalin skin baths after sun baths.....226
— — — body temperature 225
— — — insulin 223
Blood sugar and insulin in decapsulated rats 220
— — — pancreas transplantation of 524
— — — parasympathetic stimulants 365
— — content and epinephrine output during peptone poisoning 96
— — — and insulin treatment of dermatoses 117
— — — effect of guanidine hydrochloride upon.... 94
— — curve and muscular atrophy 363
— — — potassium iodide and thyroid preparations.114
— — estimations, study of.....525
— — peripheral control of, by drugs 694
— — regulations of water concentration and.....526
Calcium, maternal and foetal blood serum following injection of parathyroid extract in foetuses in utero.....532
— metabolism 229
— — in certain skin diseases...694
Carbohydrate metabolism 229
— — and adrenalectomy 209
— — — epinephrine 521
— — — endocrinopathies 1
— — — gonads 591
— — — thyroid 377
— — disturbance of 108
— tolerance and insulin.....526
Carcium and adrenaline, action of, on heart 93
Carotid body, function of.....694
Castration and creatinuria.....357
— — eunuchoidism in man.....697
— — hypophysis 823
— — metabolism 695
— — ovarian hormone injection.355
Cataract and postoperative tetany 535
Childhood myxedema 706
Chloralose and adrenin secretion 510
Chromaffin system of man, embryology of 352
Chromaphil tissue and interrenals 508
Clitoris as endocrine organ.....688
Corpus luteum 514
— — and female gonads.....817
— — — hysterectomy 356
— — — inhibition of ovulation.514
— — — oestrus 516
— — — pseudo pregnancy 514
— — cystological studies on....818

Cretinism, experimental 126
— in Spain (Book Review).....688
— iodine content of blood in...177

Deafness and pituitary dysfunction 245
— in endocrinopathies 1
— — thyroid disease.....377
Dementia praecox, endocrine glands and autonomic systems in 349
Diabetes 525
— and acetates 220
— — acromegaly 703
— — basal metabolism 524
— — exophthalmic goiter 127
— — gangrene 361
— — hypertension 701
— — inflammation of islands of Langerhans 529
— — insulin 360, 364
— — ocular disturbance 227
— — oral pancreas preparations 824
— — pregnancy 226, 227
— — red blood cells.....364
— — vascular diseases 360
— — vitamin B 528
— hyperthyroidism and myxedema 228
— in children and bone development 115
— insipidus, and pituitary extract 699
— — diuretic substance of.....820
— — report of case.....219
— — studies on 97
— insulin and diet.....522
— — neutralizing power of blood in 527
— management of 222
— mellitus 113
— — and Addison's disease..... 89
— — — adiposity 223
— — — glycemia 221
— — — insulin 365
— — — — treatment in children 227
— — — tuberculosis 221
— — calcium and glucose tolerance in 229
— — in children 111
— — latent tolerance in.....701
— — synthalin in treatment of.116
— — unusual case of.....222
— refractory to insulin.....800
— respiratory quotient curves in diagnosis in 116
— synthalin in 112
— treatment of, by insulin and diet (Book Review) 688
— unbalanced protein diet in...114
— use of synthalin in.....118
Diabetic acidosis and leucocytosis 111
— coma and insulin 531
— — and its treatment.....224
Diabetics, blood of, and hyperglycemia 524
Dwarfism and hypophysis dysfunction 359

Edema from insulin.....501
Effect of thyroid therapy on children 833
Endemic goiter and cretinism in Spain (Book Review) 688
Endocrine diagnosis 1
— disorders related to common syndromes 214
— glands, growth of, in children 512
— — in dementia praecox.....349
— — physiological, chemical and pharmacological properties of 213
— — size inter-relationship of..353
— organs and homoplastic grafts 511
— studies in schizophrenia.....716
— — histology of, at various ages 685
— theory of Mongolian idiocy (Book Review) 685
— therapy in behavior disorder in children 98
Endocrines in general medicine.690
Endemic goiter and tuberculosis.244
— — survey of 373
Eosiniphilia in endocrine disorders 1
Ephedrine, and adrenin secretion.508
Epinephrin, action of, on capillaries and fibers of skeletal muscle 692
— — — — uterus in labor.....107
— — — — cardiac rhythms 93
— administration without anesthesia 210
— and carbohydrate metabolism.521
— — glycosuria 522
— antagonism of alkaloids to... 93
— blood pressure and intestinal motility 691, 813
— — — — intestinal motility sensitivity to 506
— calorigenic action of..... 94
— decerebration and.....507
— diabetes and peripheral tissue 228
— effect of hemorrhage upon rate of liberation of.....693
— — — in partition of food stuffs in obese and normal individuals .. 92
— — — on auricular tonus waves of turtle heart. 94

Epinephrin, hemodynamic action of 507
— oral administration of.....212
— output and blood sugar content during peptone poisoning 96
— — effect of guanidine hydrochloride upon 94
—sensitiveness at menopause... 59
Ergothioneine not hypophysis secretion 467
Estrogen, a new sex hormone...151
Eunuchoidism and castration in man 697
Exophthalmic goiter 235
— — and diabetes 127
— — — involuntary nervous system 239
— — — iodine 369
— — — lead ionization 537
— — — myxedema 55
— — — quinine 705
— — — thyroid secretion.....828
— — of peculiar type 242
— — striopallidal and bulbar symptoms in 372
Exophthalmos in case of adenomatous goiter 680

Female reproductive organs and corpus luteum 817
— sex-hormone, biological action of 517
— — — blood test 216
— — — (menformon), influence of, on mammary glands 101
Follicular extracts and sex organs 696
— — experiments with 819
— hormone in body 215
— — — menstruation 99
— liquid, "anti-masculine" action of 518
Folliculi and residual tissue of ovary, distribution of hormone between 769
Folliculine, properties of.....516
Further observations on relation between adrenals and muscular action 814

Galactose tolerance in endocrinopathies 1
— — — thyroid disease 377
Gestation period and thyroid...539
Gigantism, experimental case of.822
Glandular factors in mental growth 689
Glucose and internal secretion of pancreas 225
— effect of insulin and muscle on solutions of 523
Glutathione, adrenal content of.505
Glycemia and diabetes mellitus..221
Glycemic curve and prediabetes.366
Glycogen and insulin in decapsulated rats 220
Glycosuria after epinephrine....522
— and pregnancy 363
Goiter, adenomatous with exophthalmos 680
— and diseased tonsils 234
— congenital, and iodine.....539
—geographical distribution of..238
— iodine content of blood in....177
— Langhan's proliferating 122
— malignant, symptoms and treatment of 704
— new type of and iodine 241
— nodular, with hyperthyroidism 537
— patients and congestive heart failure 237
— spontaneous decrease of, in Spain 242
Gonads, activation of secretion of, by pituitary 517
— and metabolism 591
— endocrine functions of.....591
— failure, diagnosis and treatment of 591
— stimulating hormone of anterior pituitary 215
Gonadal dysfunction and sugar tolerance test 117
Graft therapy in hypophysectomy 451
Graves' disease, essential nature of 190
— — ophthalmoplegia in 834
Growth and pineal feeding.....791
Guanidine intoxication and vagoirritability 704

Headache and pituitary dysfunction 245
— in endocrinopathies 1
Heart and pituitary dysfunction.245
— beat, hormone of 106
— extract of warm-blooded animals 519
— hormone 211
— — of 819
— — radiation experiments with 357
— in thyroid disease.....377
Heparin, purification and reactions as anticoagulant 512
Heredity and endocrinopathies.. 1
Hermaphroditism and impregnation 216
—in guinea-pig 101
— — man 101
— — presence of intact testis...216

Hormone action and recipient tissue 161
— control of vesicula seminals..516
— female sex 514
— — — and Allen-Doisy test...514
— in urine and pregnancy.....513
— of the heart 819
Hypercholesterolemia and insulin 523
Hyperglycemia, action of nickel and cobalt salts on insulin....526
— and blood of diabetics.....524
— produced by diabetic blood injection 525
Hyperinsulinemia following dextrose hyperglycemia 229
Hyperthyroidism and basal metabolism 375
— — benign tumors of thyroid gland 242
— — diabetes 228
— — iodine administration 374
— — — therapy 536
— — nitrogen metabolism 369
— — nodular goiter 537
— — pigmentation of feathers..831
— — psychosis 706
— — pyelitis 534
— — surgical treatment 370
— — thyroidectomy 236
— — x-ray treatment 371
— clinical and histological study of 375
— control of, by thyroidectomy.123
— creatine in artificial.....534
— experimental 124
— of long-standing and spontaneous subsidence 237
— simulating heart disease.....242
Hypoglucemia and galegine sulphate 365
Hypoglycemia and insulin 361
— in scleroderma 352
— phosphorus content in muscular tissue during 116
Hypophamine, Alpha and Beta, properties of 671
Hypophysectomized puppy, result of replacement therapy in ...451
Hypophysis ablation, effect of insulin after 113
—and adiposity 127
— — bone fracture 98
— — dental anomalies.....109
— — epilepsy 820
— — glycogenesis 359
— — Raynaud's disease 107
— — thyroid, reciprocal action of 111
— — visual field in pregnancy..698
— changes in during pregnancy.359
— diuretic-antidiuretic effect of posterior lobe of 698
Hypophysis dysfunction and dwarfism 359
— extirpation and pituitary secretion 467
— extract, and growth, in castrates 521
— — — insulin output 225
— — — sulfur content 823
— — sex-determining action of..521
— glandular elements in posterior lobe of.....519
— graft of, after ablation.....451
— (human) pars intermedia of..129
— injection and oestrus.....821
— in pluriglandular syndromes..707
— melanophore-expanding and uterus-stimulating substance in 822
— oxytocic power of.....219
— pars intermedia of.....217
— pars tuberalis of, after ablation 467
— peduncle of the human hypophysis 218
— physiology of 688
— — and pathology of.....822
— posterior lobe of.....358
— route of absorption of active principles of posterior lobe of 467
— secretion, effect of hypophysis ablation on 467
— — route of absorption.....467
— transplantation and pregnancy 821
— tumor, and basal metabolism.520
— — and Roentgen-ray treatment 700
Hypopituitarism, case studies of.109
Hypothyroidism and constipation 235
— and pseudoepiphyses in endocrinology 355
— a rachitic-like disturbance in.126
Hysterectomy and sex cycle.....356
— relation of, to voluntary activity 100

Impregnation and hermaphroditism 216
Inner Sekretion in der ersten Lebenszeit (vor und nach der Geburt). (Book Review.)....690
Insulin 525, 527
— absorption of, from alimentary tract after pancreas ablation 115
— — — — — Thiry Vella fistulae in normal and depancreatized dogs.702
— action of, on respiratory metabolism of isolated heart..115

Insulin, action of on ferments..117
— adrenalin antagonism 361
— and acetates 220
— — Addison's disease 363
— — blood cells 701
— — — pressure 530
— — — sugar 223
— — cachexia 364
— — carbohydrate tolerance ...526
— — diabetes 360, 364, 800
— — — mellitus 365
— — diabetic coma.....531
— — experimental anaemia 528
— — glucose 366
— — hypercholesterolemia 523
— — hypoglycemia 361, 362
— — hypophysectomy 113
— — nervous system 225
— — nickel and cobalt salts....362
— — pancreas secretion 523
— — posterior lobe extract injection 526
— — red blood cells 364
— — sugar utilization 700
— — synthaline 367
— — the diabetic pancreas.....530
— — treatment of diabetes mellitus in children 227
— — vagotomy 229
— — water content of liver.....214
— blood pressure and vagus tonus 224
— coma, diagnosis of 702
— comparison of synthalin with.524
— edema, a case of 362
— effect of duodenal secretion upon secretion of 199
— — — on blood sugar of nephrectomized dogs 524
— — — upon cerebrospinal fluid 118
— glucose treatment of traumatic shock 528
— glycemia and glycogen in decapsulated rats 220
— hypersensitivity to, edema from 501
— hypoglycemia and sugar content of blood 525
— — effect of cobalt in 111
— influence on oxidases of organs 537
— initial hyperglucemic effect of.114
— injections and atrophy of subcutaneous fat 528
— intestinal injection of.....530
— in massive dosage 823
— — treatment of ulcers of leg.702
— like substances in plants and bacteria 529
— method of biological assay of.690
Insulin neutralization in the blood 527
— output and hypophysis extract 225
— reactions 112
— relation of, to ovaries and uterine hemorrhage 105
— requirements on various diets 522
— studies on crystalline.....523
— sulfur of 366
— therapy in carcinoma.....116
— thyroid antagonism 226
— treatment of dermatoses 117
Internal secretions and types of human nature 689
— — handbook of....686, 687, 688
Iodin and basal metabolism.....373
— and exophthalmic goiter.....369
— — new type of goiter 241
— — thyroxin content of the thyroid, seasonal and geographic variations in ...830
— — toxic adenoma 376
— compounds and absorption by thyroid gland.....834
— content of blood in ordinary goiters and in cretinism...177
— — — thyroid gland and its relation to glandular condition 128
— deficiency and animal nutrition and pathology 539
— — symptoms and their significance in animal nutrition and pathology 539
— preparations and axolotl metamorphosis 128
— therapy and hyperthyroidism.536
Islands of Langerhans and adrenin 825
— — — inflammation of 529
— — — hypertrophy of, with hypoglycemia 824

Kidney function in endocrinopathies 1

Langerhans, islands of after insulin 530
— — — and vagotomy 522
Langhan's proliferating goiter..122
Leukemia and basal metabolism 1
Liver, effect of insulin, thyroid-extract and adrenin upon water content of 214
— extract and pernicious anemia 359
— function and endocrinopathies 1
— — in thyroid disease.....377
— growth of, and thyroid apparatus 123
Lutein injections, effect of, on oestrous cycle 818

Malaria, latent, and adrenin....505
Male characteristics in capons and senile cocks after injection of serum from young males...215
Melanophores, effect of pituitary substances on 663
Menformon 515
— influence of, on mammary glands 101
— preparation and properties of.101
—dosages of 515
Menopause and epinephrine..... 59
Menstruation and ovulation in monkey, relation between....100
— — and pituitary dysfunction.245
— — thyroid disease 370
— in endocrinopathies 1
Mental growth, glandular factors in 689
Metabolic effect and clinical application of Collip's parathyroid hormone 230
Metabolism and castration 695
Metabolism in endocrine disorders 1
— — pluriglandular syndromes.707
— regulation of 531
Metamorphosis and pineal feeding 791
Mongolian idiocy 243,244
Mongolism (Book Review).....685
Myxedema and diabetes 228
— — Erb's familial muscular dystrophy 235
— and exophthalmic goiter..... 55
— diagnosis and cardio-vascular methods of investigation...236
— in childhood 237
Myrtillin, pancreatic insufficiency and 528

Nephrectomy, effect of insulin on blood sugar after 524
Neurine, and adrenin secretion..508
Nutrition and iodine deficiency.539

Obesity and pituitary dysfunction 245
— in endocrinopathies 1
Oestrus and parabiosis 357
— — hypophysis injection 821
— cycle and suprarenal insufficiency 816
— — — x-ray sterilization.....217
— — effect of lutein injections on 818
— — occurrence of, after x-ray sterilization 102
— producing autacoid 193
— — hormone 356
— — — biological assay of.....690
— prolonged by ovarian extracts.105
Ovarian and placental hormone effects in normal, immature, Albino rats 804
— extracts, protracted oestrus induced by 105
— feeding and oestrus.....193
— follicular hormone and sterility 695
— — — in blood of pregnant women 104
— grafts and anterior pituitary.215
— hormone 105
— — and follicular liquid.....518
— — — oestrus cycle 356
— — — uterine and mammary development 355
— — effects of, in immature rats 804
— — extracted from urine 697
— — in water soluble form.....100
— secretion and tumor incidence 102
— substance, and sugar utilization 700
Ovariectomy and hypophysis extract 219
Ovaries and metabolism 591
— experiments on isolated.....696
Ovary and insulin 105
— — metabolism 1
— changes in after x-rays.....214
— distribution of, hormone of...769
— histological study of.....106
— hormone, vaginal smear assay of 760
— in pluriglandular syndromes..707
— of mole, cyclic changes in....355
— studies on internal secretion of 516
— transplantation, technique of.491
— traumatization and spontaneous activity 106
Ovulation and menstruation in monkey, relation between....100
— inhibition by corpus luteum..514
Ovum and hormones.....217
Oxytocin, effect of, on melanophores 663
— properties of; tests for.....671

Pancreas ablation, absorption of insulin after 115
— — and glucose administration 360, 365
— — — hypophysis 822
— — — insulin absorption 702
— — — voluntary activity.....703
— — glycemic changes after pancreatic grafts and glucose ingestion 824
— and duodenal secretion.....199
— — glucose 225
— carcinoma of islands of.....825

Pancreas preparations and diabetes 824
— relations of internal and external secretion 523
— secretion, glycolytic factor in blood 522
— — regulation of 824
— transplantation and blood sugar 524
— — — control of internal secretion of pancreas..222
Parabiosis and oestrus.....357
Paraganglia in man, topography of 352
— of abdomen and subperitoneal nervous plexus 351
Parathormone and infantile tetany 368
Parathyroid ablation and hypophysis 822
— — — protective action of blood 367
— — — calcium and phosphorous 231
— — inter-relations of calcium, phosphorus and sugar after 827
— — of, and cod liver oil diet..532
— activity, standardization of...367
— and calcium contents in foetal life 532
— — solar irradiation 826
— — thyroid ablation and differential development 124
— — thyroid in growth of heart and lungs 123
— extract and distribution of calcium 118
— — and infantile tetany 533
— — — nephrosis 369
— — — sunlight, blood calcium.797
— — — tetany 533
— — in infantile tetany.....231
— — — treatment of tropical sprue 120
— — — myasthenia gravis and creatinuria 367
— hormone, action of in bone transplantation 367
— — and blood coagulability...119
— — and calcification of fracture callus 121
— — (Collip's), metabolic effect and clinical application of 230
— — effect of, on gastric secretion 119
— — method of biological assay of 690
— in swine, topography of.....230
— morphology, embryology and anatomy of 686
Parathyroid, ossification and growth 533
— physiology 687
— preservation 120
— tetany and CO_2 administration 368
— — — thyroid hormone.....832
— — — tissue changes 826
— — — vago-irritability 704
— — control of, by kaolin.....119
— Vater Pacinian corpuscles in.704
Parathyroidectomy and ultraviolet light 81
Pars intermedia of human hypophysis 129, 217
Peduncle of human hypophysis..218
Personality and endocrine glands 689
Phosphorous and blood fat, variations of, in reproductive cycle 104
Pineal ablation and gonads.....231
— discussion of 688
— feeding and frog metamorphosis; growth 791
— gland, tumors of.....121
— pathology 368
Pituitary 699
— activation of gonadal secretion 517
— and blindness 245
— — blood pressure 245
— — deafness 245
— — headache 245
— — heart 245
— — menstruation 245
— — metabolism 1
— — obesity 245
— — occupation 245
— — parasthesias 245
— — sterility 245
— — thyroid 245
— — tonsils 245
— antidiuretic effect of extract of 699
— control of ovary by.....217
— dysfunction and sugar tolerance test 117
— effect of, on insulin 526
— extract and behavior disorders in children 98
— — — muscle contraction 511
— — — thyroparathyroid ablation 519
— — effect of, on uterus in labor 107
— — method of biological assay of 690
— hyperglycemia, mechanism of.218
— oxytocic and pressor principles, effect on water diuresis in man 496
— posterior, active principles of.671
— separation of two active principles of posterior lobe of..699

Pituitary size, sex difference and intestinal length 203
Pituitrin and distribution of injected fluid 110
— effect of, on melanophores...663
— hyperglycemia and origin of glucose 519
— in spinal fluid 520
— secretion and diuretics 357
Placenta, discussion of.....688
Placental extract, experiments with 819
— hormone, effects of, in immature rats 804
Pluriglandular disorders and metabolism 1
— disturbance and pseudoepiphyses 355
— syndromes; metabolism in; diagnosis of; treatment of.707
Pregnancy and adrenal gland...506
— — diabetes 226, 227
— — glycosuria 363
— — hypophysis 822
— — — transplantation 821
— — hormone in urine 513
— — hypophysis 359
— — superovulation 216
— — thyroid 828
— pseudo-, and corpus luteum..514
Prostate ablation and sex life of male rat 697
Pseudoepiphyses in endocrinology 355
Pseudohermaphroditism and metabolism 591
Pseudonephritis in thyroid disease 377
Puberty praecox, mental development of children showing signs of 98
Raynaud's disease and hypophysis 107
Reproduction in birds, physiology of 104

Scleroderma, hypoglycemia in...352
Scurvy, and thyroid histology in.534
Secretin, effect of, on insulin secretion 199
Sex-determining action of hypophysis extract 521
— difference, intestinal length and pituitary size.....203
— differentials, theory of.....103
— glands, studies on.....686
— hormone content of blood in women 515
— hormone, Estrogen 151
— — quantitative action of.....514
— organs and follicular extracts.696
Spleen and red bone marrow, effect of, on blood forming centers 122
— — sedimentation velocity of red corpuscles 97
— growth of, and thyroid apparatus 123
Steinach operation 357
Sterility and endocrinopathies... 1
— — ovarian follicular hormone 695
— — pituitary dysfunction 245
— — thyroid disease 377
Sugar in animal body 220
— metabolism, effect of adrenalin on 157
— tolerance, as aid to diagnosis.117
— utilization and iodine compounds 834
Suprarenal, see also adrenal.
— ablation and thyroidectomy..815
— adrenalin content of, in chick embryo 342
— and regulation of blood pressure 505
— capsule, primary tumor of...506
— diet, effects of, on organism and sex function 509
Superovulation and pregnancy ..216
Synthalin, action of.....524, 529
— and insulin 367
— in diabetes 112, 118
— with insulin action.....112

Testes ablation and pineal.....231
— and metabolism 1, 591
— — sedimentation of red corpuscles 97
— in pluriglandular syndromes..707
— transplantation, technic of...491
Testicular transplants, importance of site of attachment of.819
Testicle grafting in Triton Cristatus 513
— (monkey) grafts in man.....103
Testicular grafts in Triton.....695
— substance and sugar utilization 700
Tetany and chronic diarrhea...533
— postoperative, and cataract...535
Thymic death in infants.....122
— enlargement and atelectasis..232
Thymus and bone fracture..... 98
— — chloroform narcosis 232
— diagnosis and treatment in enlargement of 233
— extract and thyroparathyroid ablation 519
— physiology and anatomy of..232
Thyroid ablation and hypophysis 822
— — — iodin medication 371
— — — injury to recurrent laryngeal nerve 238

Thyroid ablation and phagocytosis 832
——— spontaneous activity ...536
——— thyrotoxicosis 371
——— tissue respiration 828
——— toxins in suprarenalectomized rats 815
— and calcium metabolism 233
—— carbohydrate metabolism..377
—— distribution of iodine, sugar and amino acids in blood 535
—— feather development..831, 832
—— hypophysis, reciprocal action of 111
—— intersexual type 373
—— metabolism 1
—— parathyroid ablation and differential development.124
——— in growth of heart and lungs 123
—— pituitary dysfunction.....245
—— pregnancy 828
—— sedimentation of red corpuscles 97
— apparatus and growth of liver, kidneys and spleen 123
— deficiency without myxedema.377
— desiccated, and sugar utilization 834
— diagnostic study of 377
— disease, 100 cases of, analyzed 377
—— basal metabolism in; circulation in 377
—— and acid base equilibrium.375
——— heart studies 371
——— menstruation 370
——— psychoses 377
—— atypical 377
—— blood morphology and chemistry in 377
—— galactose tolerance in.....377
—— physical measurements in.377
—— urine in; liver in; sterility in 377
— dysfunction and fever 240
——— sugar tolerance test....117
— extract and abortion.....376
—— and autonomic excitability of heart 535
——— nervous system.....535
——— behavior disorders in children 98
——— cachexia 364
——— muscle contraction 511
——— water content of liver..214
—— method of biological assay of 690
— factor in deafness.....377
— feeding and body weight....831
—— and growth of guinea pig.705
Thyroid feeding, effect of, on thymus, testicle and thyroid..705
— gland and absorption of iodine compounds 834
—— basal metabolism and work 833
—— in infections 773
——— the effect upon the basal metabolic rate 773
——— young adults 374
—— substance implantations...126
— histology of, in scurvy.....534
— hormone and parathyroid tetany 832
— infections and toxemias 369
— influence of, in experimental rickets 126
—— on oxidoses of organs.....537
— insulin antagonism 226
— in pluriglandular syndromes..707
— iodine content of 128
— medication and stammering..534
— morphology, embryology and anatomy of 686
— physiology 687
—— and anatomy of.....232
— preparations and blood sugar curve 114
— radiation therapy in malignant diseases of 127
— relation of hyperthyroidism and benign tumors of 242
— secretion and exophthalmic goiter 828
— therapy, effect of on children.833
—— in children 833
— treatment and nephrosis.....369
— substance and sugar metabolism 700
Thyroidectomy and adrenalin...815
— and hypophysis extract 219
—— iodine 239
—— water absorption 533
— control of hyperthyroidism by 123
— for hyperthyroidism 236
— indications for 244
Thyroparathyroid ablation and cod-liver oil feeding 829
——— ligation of common bile duct 826
——— ultraviolet light 829
Thyroparathyroidectomy and ultraviolet light 81
Thyroxin, action of natural and synthetic 122
— and basal metabolism 537
—— glands of internal secretion 375
—— nitrogenous metabolism...234
—— respiratory metabolism ...234

Thyroxin and sugar utilization..834
— content of the thyroid, seasonal and geographic variations in 830
— depressant of cell division... 65
— effects on adrenals of mouse..323
— — on teeth of newborn rats..238
— relation of, to sympathetic nervous system 122
Thymus and feather development 831, 832
— feeding and body weight.....831
Toxic adenoma and iodine.....376
Transplantation and sex character in earth-worm 214

Ultraviolet light on parathyroidectomized rats 81
Uremia, and adrenal cortex.....509
Urine and gonads.....591
— in endocrinopathies 1
Uterus, activity and working power of muscles of, in nonpregnant sow 100
— and growth hormones.....161
— as endocrine organ 688

Vagina and growth hormones...161
— as endocrine organ.....688
Vagotomy, effect of on islets of Langerhans 522
Vaginal smear method for assay ovarian hormone 760
Vasopressin, effect of, on melanophores 663
— properties of; tests for.....671
Vital function tests in endocrinology 1

Weight and gonads 591

X-ray, effect of on adrenals.....335